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CONTENTS OF VOLUME 52

JULY, 1933. NUMBER 1

PAGE

Diagnosis of Gonococcus Endocarditis. Philip Solomon, M.D.; David Hurwitz, M.D.; Martin Woodall, M.D., and Marion E. Lamb, Boston... 1

Factors Causing Clinical Jaundice in Heart Disease. M. A. Kugel, M.D., and S. S. Lichtman, M.D., New York..... 16

Premature Left Ventricular Beats from Electrical Stimulation of Exposed Human Heart. Clayton J. Lundy, M.D., and Charles M. Bacon, M.D., Chicago..... 30

Influence of Sclerotic Arterial Wall on Blood Pressure Measurements: Report of Case with Calcification of One Radial Artery. David Ayman, M.D., Boston, and A. Krakower, M.D., Montreal, Canada..... 33

Clinical Studies of Respiration: I. Plethysmographic Study of Quiet Breathing and of the Influences of Some Ordinary Activities on the Expiratory Position of the Chest in Man. J. A. Greene, M.D., Iowa City, and H. C. Coggeshall, M.D., Indianapolis..... 44

The Question of the Presence of a Pressor Substance in the Blood in Essential Hypertension. G. E. Wakerlin, M.D., Ph.D., and H. D. Bruner, S.B., Louisville, Ky..... 57

Treatment of Neurosyphilis: Review of Results in Six Hundred and Eighty Patients. H. Hanford Hopkins, M.D., Baltimore..... 66

Hyperinsulinism: Report of a Case of Spontaneous Hypoglycemia, with Studies in Dextrose Tolerance. Eugene Ziskind, M.D., Los Angeles.... 76

Blood Cholesterol in Thyroid Disease: II. Effect of Treatment. Lewis M. Hurxthal, M.D., Boston..... 86

Physical Characteristics of Residues from the Small Intestine. Harry Landt, M.D., and Kate Daum, Ph.D., Iowa City..... 96

Influence of Sodium Nitrite on the Cardiovascular System and on Renal Activity in Health, in Arterial Hypertension and in Renal Disease. Soma Weiss, M.D., and Laurence B. Ellis, M.D., Boston..... 105

A Comparative Study of Blood Cultures Taken with Kendall and Routine Mediums. Charles K. Friedberg, M.D., New York..... 120

An Unusual Blood Group. Mable M. Wilhelm, B.A., and Edwin E. Osgood, M.D., Portland, Ore..... 133

Clinical Significance of Latent Pulmonary Tuberculosis. F. Maurice McPhedran, M.D., and Eugene L. Opie, M.D., New York..... 137

Function of the Liver: An Appraisal of the Modified Dextrose Tolerance Test. Henry T. Ricketts, M.D., Chicago..... 147

Correspondence:
"The Relation of Withdrawal of Cerebrospinal Fluid to the Body Temperature."..... 158

Book Reviews..... 159

AUGUST, 1933. NUMBER 2

Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris: III. Early Results in Various Types of Cardiovascular Disease and Coincident Pathologic States Without Clinical or Pathologic Evidence of Thyroid Toxicity. Herrman L. Blumgart, M.D.; Joseph E. F. Riseman, M.D.; David Davis, M.D., and David D. Berlin, M.D., Boston..... 165

AUGUST—Continued

PAGE

Clinical Studies of Respiration: II. Influence of Determination of Basal Metabolism on Respiratory Movements in Man, and Effect of These Alterations on Calculated Basal Metabolic Rate. J. A. Greene, M.D., Iowa City, and H. C. Coggeshall, M.D., Indianapolis 226

Benign and Malignant Neutropenia: Present Status of Knowledge of This Condition, with Report of Four Cases. Regena C. Beck, M.D., Richmond, Va. 239

Cholesterol and Lecithin Phosphorus in the Plasma of Anemia Other Than Pernicious Anemia: Influence of Therapeutic Measures on These Constituents. Gulli Lindh Muller, M.D., and Clark W. Heath, M.D., Boston 288

Effect on the Reflexes of the Carotid Sinus of Raising the Intracranial Pressure. C. M. Guernsey, B.S.; S. A. Weisman, M.D., and F. H. Scott, M.B., Ph.D., Minneapolis 306

Absorption of Dextrose by Rectum. William S. Collens, M.D., and Louis C. Boas, M.D., Brooklyn 317

Pleurisy in Rheumatic Fever: Clinical Observations. Walter K. Myers, M.D., and Eugene B. Ferris, Jr., M.D., Boston 325

Book Reviews 338

SEPTEMBER, 1933. NUMBER 3

Ultimate Results of Thoracoplastic Operations in Pulmonary Tuberculosis. J. J. Wiener, M.D., and Maurice Fishberg, M.D., New York 341

Iron in Human Blood. Adolph Sachs, M.D.; Victor E. Levine, M.D., and Abraham Appelsis, B.S., Omaha 366

Insensible Perspiration: Its Relation to Basal Metabolism. Gale E. Wilson, M.D., Seattle 378

Therapeutic Application of Acidophilus Milk in Simple Constipation: A Report of Thirty-Six Cases. Louis Weinstein, Ph.D.; James E. Weiss, B.S., and Leo F. Rettger, Ph.D., New Haven, Conn., and Maurice N. Levy, M.D., Bridgeport, Conn. 384

Cinchophen Poisoning: Report of Two Cases with Histologic Observations. H. H. Permar, M.D., and H. D. Goehring, M.D., Pittsburgh 398

Fatty Infiltration of the Myocardium. O. Saphir, M.D., and M. Corrigan, M.D., Chicago 410

Cardiac Weights. Victor Levine, M.D., and James G. Carr, M.D., Chicago .. 429

Clinical Studies of Respiration. J. A. Greene, M.D., Iowa City:
III. Influence on the Expiratory Position of the Chest in Man of an Inspired Air Which Is Low in Oxygen and High in Carbon Dioxide, and of Resistance to Inspiration and to Expiration 447
IV. Some Observations on Cheyne-Stokes Respiration 454

Effect on Idiopathic Hypochromic Anemia of Beef Steak (Hamburger Steak) Digested with Normal Gastric Juice. Richard T. Beebe, M.D., Albany, N. Y., and M. M. Wintrobe, M.D., Baltimore 464

Cinchophen Toxicosis: Results of Experimental Subacute and Chronic Cinchophen Poisoning. A. J. Lehman, Ph.D., and P. J. Hanzlik, M.D., San Francisco 471

Book Reviews 493

OCTOBER, 1933. NUMBER 4

Primary Carcinoma of the Lung, with Special Reference to Incidence, Early Diagnosis and Treatment. Allan J. Hruby, M.D., and Henry C. Sweany, M.D., Chicago 497

Diffuse Ulceration of the Esophagus and Trachea Associated with Diabetes Mellitus: Absence of Arteriosclerosis. Porter P. Vinson, M.D., and Russell M. Wilder, M.D., Rochester, Minn 541

OCTOBER—Continued

PAGE

Human Capillaries in Health and in Disease. Irving Sherwood Wright, M.D., and A. Wilbur Duryee, M.D., New York 545

Monosodium Thyroxine, Desiccated Thyroid and an Impure Sodium Salt of Thyroxine: Comparison of Their Effects when Administered Orally with the Effect of Thyroxine Injected Intravenously in an Alkaline Solution. Willard O. Thompson, M.D.; Phebe K. Thompson, M.D., and Lois F. N. Dickie, B.M., Chicago 576

Benign Familial Polycythemia. Anthony Spodaro, M.D., and Claude E. Forkner, M.D., Boston 593

Temperature of the Gastro-Intestinal Tract: The Effect Thereon of Hot and Cold Foods and of Physical Therapeutic Agents. Joseph S. Hepburn, Ph.D.; Harry M. Eberhard, M.D.; Rowland Ricketts, M.D., and Charles L. W. Rieger, M.D., Philadelphia 603

Changes in Gastric Acidity in Peptic Ulcer, Cholecystitis and Other Diseases Analyzed with the Help of a New and Accurate Technic. Frances R. Vanzant, M.D.; Walter C. Alvarez, M.D.; Joseph Berkson, M.D., and George B. Eusterman, M.D., Rochester, Minn 616

Nitrogen and Sulphur Metabolism in Bright's Disease: IV. Retention of Urea in the Nephrosis Syndrome. G. P. Grabfield, M.D., Boston 632

Urea Clearance Test in Pregnancy. A. Cantarow, M.D., and G. Ricchiuti, M.D., Philadelphia 637

Book Reviews 647

NOVEMBER, 1933. NUMBER 5

Periodicity of Carbohydrate Metabolism and Rhythmic Functioning of the Liver: Their Significance in the Treatment of Diabetes with Insulin. Jakob Möllerström, M.D., Stockholm, Sweden 649

Epilepsy and Convulsions in Diabetes. William R. Jordan, M.D., Boston ... 664

Toxic Cirrhosis Caused by Cinchophen. James F. Weir, M.D., and Mandred W. Comfort, M.D., Rochester, Minn 685

Studies on Digitalis in Ambulatory Patients with Cardiac Disease: V. Further Observations on the Nature of the Cumulation of Digitalis. Harold L. Otto, M.D.; Harry Gold, M.D., and Charles R. Messeloff, M.D., New York 725

Experimental Renal Insufficiency Produced by Partial Nephrectomy: II. Relationship of Left Ventricular Hypertrophy, the Width of the Cardiac Muscle Fiber and Hypertension in the Rat. Alfred Chanutin, Ph.D., and Edwin E. Barksdale, M.D., University, Va 739

Electrocardiographic Study of Coronary Occlusion: Further Observations on the Use of Chest Leads. Francis Clark Wood, M.D.; Samuel Bellet, M.D.; Thomas M. McMillan, M.D., and Charles C. Wolferth, M.D., Philadelphia 752

A Simple Method of Producing Vasodilatation in the Lower Extremities, with Reference to Its Usefulness in Studies of Peripheral Vascular Disease. Eugene M. Landis, M.D., and John H. Gibbon, Jr., M.D., Philadelphia .. 785

Effect of Alkali on the Absorption of Thyroxine from the Gastro-Intestinal Tract, with a Note on the Comparative Effects of Synthetic and "Natural" Thyroxine Injected Intravenously. Willard O. Thompson, M.D.; Phebe K. Thompson, M.D.; Lois F. N. Dickie, B.S., and Joseph M. Alper, M.D., Chicago 809

Book Reviews 821

DECEMBER, 1933. NUMBER 6

Production of Reticulocytes, Erythrocytes and Hemoglobin in Anemia: Their Response to Certain Types of Therapy. William P. Murphy, M.D., Boston 829

DECEMBER—Continued

PAGE

Macrocytic Anemia in Disease of the Liver. John Van Duyn 2d, M.D., Syracuse, N. Y. 839

Aleukemic Myelosis. C. W. Baldridge, M.D., and W. M. Fowler, M.D., Iowa City 852

Peripheral Vascular Phenomena: III. The Peripheral Pulse Volume in Occlusive Arterial Diseases. George W. Scupham, M.D., and Carl A. Johnson, M.D., Chicago 877

Lobar Atelectasis as a Cause of Triangular Roentgen Shadows in Bronchiectasis. W. P. Warner, M.D., and Duncan Graham, M.D., Toronto, Canada 888

Intra-Uterine Rheumatic Heart Disease. R. W. Kissane, M.D., and R. A. Koons, M.D., Columbus, Ohio 905

Adiposity of the Heart: A Clinical and Pathologic Study of One Hundred and Thirty-Six Obese Patients. Harry L. Smith, M.D., and Fredrick A. Willius, M.D., Rochester, Minn 911

Insulin Resistance in Diabetes Mellitus. Cyril M. MacBryde, M.D., St. Louis 932

Skin Lesions of Pellagra: An Experimental Study. Tom D. Spies, M.D., Cleveland 945

Changes in Blood Pressure of Young Men Over a Seven Year Period. Harold S. Diehl, M.D., and Meredith B. Hesdorffer, M.D., Minneapolis .. 948

Heredity in Hypertension: A Statistical Study. William Allan, M.D., Charlotte, N. C. 954

Polytropous Enteronitis (Acute Infectious Gastro-Enteritis, Spencer's Disease): Is It a Form of Influenza? H. A. Wildman, M.D., Imlay City, Mich. 959

Uncomplicated Syphilitic Aortitis: Diagnosis, Prognosis and Treatment. Joseph Earle Moore, M.D., Baltimore, and P. F. Metildi, M.D., Rochester, N. Y. 978

Correspondence:
Modified Dextrose Tolerance Test 984

Book Reviews 991

General Index 995

JUL 20 1933

VOLUME 52 NUMBER 1

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CONTENTS OF PREVIOUS NUMBER

JUNE, 1933. NUMBER 6

Mechanism of Edema of the Renal Type: Study on Basis of Changes in Water Content of Blood and in Protein Content of Blood Plasma During Cycle of Edema in Children. William B. McClure, M.D.; Carol Becker de Takáts, B.S., and Winifred Franz Hinman, M.S., Chicago.

Congestive Heart Failure and Angina Pectoris: The Therapeutic Effect of Thyroidectomy on Patients Without Clinical or Pathologic Evidence of Thyroid Toxicity. Herrman L. Blumgart, M.D.; Samuel A. Levine, M.D., and David D. Berlin, M.D., Boston.

Nature of Skin Reactions Produced by Heat-Inactivated Poliomyelitis Virus: Reaction of Persons Convalescing from Poliomyelitis and of Normal Persons to Intracutaneous Injections of the Heat-Inactivated Virus. Albert B. Sabin, M.D.; William H. Park, M.D., and Claus W. Jungeblut, M.D., New York.

Excretion of Nitrogen by Obese Patients on Diets Low in Calories, Containing Varying Amounts of Protein. Robert Wood Kenton, M.D., and Dorothy Dickens, A.B., Chicago.

Histamine Test Meals: An Analysis of Nine Hundred and Eighty-Eight Consecutive Tests. W. Scott Pollard, M.D., San Francisco.

Peptic Ulcer: VIII. Results of Medical and Surgical Treatment of Patients in Rural Districts and in Small Towns. Charles Bruce Morton, M.D., University, Va.

Effect of Stimulation of Visceral Nerves on Coronary Flow in Dogs. Josephine Hinrichsen, M.S., and A. C. Ivy, Ph.D., M.D., Chicago.

Auricular Flutter with Complete Auriculoventricular Block in a Patient with Coronary Disease. Aaron E. Parsonnet, M.D., C.M., and Sol Parent, M.D., Newark, N. J.

Standardization of Chest Leads and Their Value in Coronary Thrombosis and Myocardial Damage. Arthur M. Hoffman, M.D., and Everett Delong, M.D., Los Angeles.

Electrocardiographic Studies of the Dying Human Heart, with Observations on the Intracardiac Injection of Epinephrine; Report of Twenty-Five Cases. J. Fletcher Hanson, M.D.; W. K. Parks, M.D., and Ruskin G. Anderson, M.D., Atlanta, Ga.

Diffuse Amyloidosis: Three Unusual Cases; a Clinical and Pathologic Study. Edwin G. Bannick, M.D.; John M. Berkman, M.D., and Donald C. Beaver, M.D., Rochester, Minn.

Book Reviews.

General Index.

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Archives of Internal Medicine

VOLUME 52 JULY, 1933 NUMBER 1

DIAGNOSIS OF GONOCOCCUS ENDOCARDITIS

PHILIP SOLOMON, M.D.

DAVID HURWITZ, M.D.

MARTIN WOODALL, M.D.

AND

MARION E. LAMB

BOSTON

Cases of gonococcus endocarditis have been reported not infrequently in the literature. Up to 1912, according to McCants, there were a hundred cases published. Since 1912 we have been able to collect forty-eight cases. Table 1 summarizes the evidence on which the diagnosis of these cases was made. The two cases which had the most complete diagnostic evidence were those of Grenet, Laurent, de Pfeffel and Levent, and of Riecker. In these cases the blood culture, bacteriologic morphology, cultural characteristics, fermentation and agglutination reactions were all positive. Huebschmann's case had a positive history, blood culture, postmortem culture, bacteriologic morphology and cultural characteristics. There were four cases that had a positive history, blood culture, bacteriologic morphology and cultural characteristics (Thayer, case 11, Laserre, Dwyer, Kramer and Smith). Two cases (Vander Veer and Kirkland) had a positive history, postmortem culture, bacteriologic morphology and cultural characteristics, but a negative blood culture. Nine cases had positive blood cultures and two other positive findings. Two cases had positive blood cultures and one other positive finding. Five cases did not have positive blood cultures, but did have three other positive findings. Ten cases did not have positive blood cultures, but did have two other positive findings. Thirteen cases had nothing on which to base the diagnosis of gonococcus endocarditis except the presence of clinical endocarditis and the history of gonorrhea.

In the case that we were recently able to study carefully, the diagnosis of acute endocarditis was evident clinically and was demonstrated at autopsy. Bacteriologically, the organism grown from the blood stream and from the vegetation on the aortic valve post mortem was identified as a gonococcus by its morphologic and cultural characteristics, fermentation reactions, agglutination, precipitin and complement fixation

From the Neurological Service and Department of Pathology, Boston City Hospital.

TABLE 1.—*Evidence for Diagnosis of Gonococcus Endocarditis in Patients with Clinical Signs of Endocarditis*

Author	History of Gonorrhea	Blood Culture	Postmortem Culture	Bacteriologic Morphology	Cultural Characteristics	Fermentation Reactions	Agglutination	Precipitin	Complement Fixation	Comments
Thayer: Case 1	..	—	+	+	..	..	..	..	.....	Prostatic fluid showed gram-negative diplococci
Case 2	..	—	..	+	..	..	..	..	.....	Necropsy performed 5 days after death
Case 3	..	—	+	+	..	..	..	..	.....	
Case 4	..	+	..	+	+	..	..	..	.....	
Case 5	+	+	..	+	..	..	..	..	.....	
Case 6	+	—	—	+	..	..	..	..	.....	
Case 7	+	+	..	+	..	..	..	..	.....	Postmortem smear, but no culture
Case 8	..	+	..	+	..	..	..	..	.....	Postmortem smear, but no culture
Case 9	..	+	..	+	..	..	..	..	.....	Postmortem smear, but no culture
Case 10	+	—	..	..	..	..	..	..	.....	No bacteriologic examination at necropsy
Case 11	+	+	..	+	+	..	..	..	.....	No bacteriologic examination at necropsy
Case 12	+	—	..	..	..	..	..	..	.....	No bacteriologic examination at necropsy
Case 13	+	—	..	..	..	..	..	..	.....	
Navarro, Pueyrredón and Elizalde	+	—	..	+	..	..	..	..	.....	Pus smeared; no bacteriologic examination post mortem
Laserre	+	+	..	+	+	..	..	..	.....	
Berner	+	—	..	+	..	..	..	..	Patient's blood against known gonococci +	Postmortem smear, but no culture
Thayer and Blumer	..	+	..	+	+	..	..	..	.....	Postmortem smear, but no culture
Vander Veer	+	—	+	+	+	..	..	..	.....	
Huebschmann	+	+	+	+	+	..	..	..	.....	
Külbs	+	..	+	+	..	..	..	..	.....	
Dwyer	+	+	..	+	+	..	..	..	.....	No postmortem bacteriology
Johnston and Johnston	+	—	..	+	..	..	..	..	.....	Postmortem smear, but no culture

Lindau	+	—	+	+	..	..	..	..	.....	
Buquet and Jaureguy	+	..	..	+	..	..	..	..	.....	
Edwards	+	—	..	+	..	..	..	..	.....	Postmortem smear, but no culture
Aubertin and Gambillard	+	—	..	..	..	..	..	..	.....	Recovery after antigonococcus serum
Haase: Case 1	+	..	..	+	..	..	..	..	.....	Smear but no culture post mortem
Case 2	+	—	—	+	..	..	..	..	.....	
Schaeffer and Baron	+	..	..	..	..	..	..	..	.....	Spinal fluid culture negative; recovery
Proschaska (3 cases)	+	+	..	+	..	..	..	..	.....	
Kramer and Smith (3 cases...)	+	2 = —, 1 = +	..	+	+	..	..	..	.....	
Charvet and Lesieur	+	..	?	..	..	..	..	..	.....	Postmortem cultures showed streptococcus; gonococcus from urethra
Mouisset and Chalier	+	..	..	..	..	..	..	..	.....	
Klein	+	—	..	..	..	..	..	..	.....	
Bard, Langeron and Gardère	+	..	..	..	..	..	..	..	.....	
Lupu and Stoënesco	+	—	..	..	..	..	..	..	.....	No bacteriology post mortem
McCants: Case 1	..	—	..	+	..	..	..	..	.....	
Case 2	..	..	..	+	..	..	..	..	.....	Smear obtained post mortem, but no culture
Grenet, Laurent, de Pfeffel and Levent	+	+	..	+	+	+	+	..	.....	Agglutination with antimeningococcus was negative; smear obtained post mortem positive
Riecker	..	+	—	+	+	+	+	..	.....	
Kirkland	+	—	+	+	+	..	..	..	.....	
Perry	+	+	..	+	..	..	..	..	.....	Patient recovered
Gertzog and Kuzmin	+	—	..	..	..	..	..	..	Patient's blood against known gonococci +	Mitral vegetation post mortem; postmortem smear
Hoffman and Taggart	..	+	..	+	+	..	..	..	.....	Postmortem smear showed gram-negative intracellular diplococci; no culture post mortem
Case herein reported	..	+	+	+	+	+	+	+	Organism against antigonococcus smear +	

reactions. As meningococcus endocarditis may occur without meningitis (Bancker and Lorentz), we believe that the aforementioned procedures are of value in the positive identification of the gonococcus in a case of endocarditis.

REPORT OF A CASE

Clinical History.—G. W., a Negress, aged 20, was admitted to the maternity ward of the Boston City Hospital on Jan. 29, 1931. The past history was essentially irrelevant. She had had two previous normal pregnancies. There was no history of tonsillitis, chorea, rheumatic fever, shortness of breath, edema, palpitation or precordial pain. The date of the last menstruation was May 1, 1930. She had been followed in the prenatal clinic, where her pregnancy proceeded uneventfully. It was noted that the patient had a systolic murmur at the mitral area. There were no toxic symptoms, and no bleeding. The baby was active. The patient was admitted to the hospital with labor pains of five hours' duration. She gave a history of a cold in the head for the past ten days. The temperature on entry was 101 F., and the pulse rate, 90 per minute. Obstetric examination showed signs of a full-term pregnant uterus.

Examination.—The day following admission the patient delivered a normal baby without anesthesia. The delivery was natural in every way. The placenta and membranes were intact. Physical examination at this time revealed nothing abnormal. There were no heart murmurs. On the third day post partum, the temperature was again 101 F., the pulse rate, 120, and the respiratory rate, 24. At this time, a productive cough developed, and the patient raised thick grayish mucoid material. No blood was noticed. A medical consultant at this time reported a few crepitant râles at the right base posteriorly and extending up into the right axilla. There were no signs of frank consolidation, and the opinion was expressed that the patient probably had an acute upper respiratory infection with some bronchopneumonia. At this time the patient was eating well and sleeping well. She was digitalized and then put on a maintenance dose of digitalis daily. On February 4, a systolic murmur reappeared in the mitral area and remained localized there. On February 6, the patient coughed up frank bloody sputum. During the next two days, she raised about 3 ounces (89 cc.). On February 8, the bloody character of the sputum subsided. The patient had no complaints except for cough. About 11:30 a. m. on February 10, twelve days after entry, the patient had a severe chill which lasted about fifteen minutes. When seen immediately afterward, she had complete right hemiplegia involving the leg, arm, palate, tongue, face and eyes. There was paralysis of lateral gaze to the right. The patient did not respond to questioning, although she appeared conscious and seemed mentally alert. She appeared to have a complete aphasia. Reflexes were present, but were diminished in the right arm and absent in the right leg, with a suggestively positive Babinski sign on that side. There was no stiff neck or Kernig sign, and the pupils reacted normally. A pelvic examination revealed no abnormality. The blood pressure was normal. Examination of the heart showed no enlargement to percussion. The sounds were regular and of good quality. A long systolic murmur was audible throughout the precordium, and a questionable diastolic murmur was present in the aortic area. The patient was transferred to the neurologic service for study.

A complete examination at this time revealed, in addition to the foregoing findings, the following: The patient was a well developed and nourished young Negress. The throat was injected; the tongue was coated, and the skin was warm and moist. There was diminished expansion of the right side of the chest, with diminished tactile fremitus and diminished resonance on that side. Crepitant râles were heard over the base of the left lung. The systolic murmur was present

throughout the precordium, but was loudest in the aortic area. A diastolic murmur was also heard in the aortic area, transmitted to the neck. No petechial spots could be found. There were a complete right hemiplegia and a complete motor aphasia, with a large sensory element. The patient could apparently understand spoken language only slightly. She could not carry out simple commands, although she seemed to understand the meaning of gestures and facial expressions. The abdominal reflexes were absent. There was a definite Babinski sign on the right.

Laboratory Work.—The Kahn and Wassermann reactions of the blood were negative. On February 3, the white blood count was 15,000 per cubic millimeter; on February 5, a blood culture was negative. On February 9, the white count was 16,000 per cubic millimeter; examination of the sputum showed it to be nonfoul; it contained no gross blood, free particles or acid-fast organisms, gram-positive diplococci were predominant; no Vincent's organisms were seen.

On the neurologic service, lumbar punctures showed the results given in table 2.

In all the lumbar punctures, the dynamics were normal. In each tap, the first fluid removed seemed to have more blood in it than the last. After centrifugation there was xanthochromia in the supernatant fluid. The nonprotein nitrogen in a specimen taken on February 11 was 24 mg. Smears showed no organisms. On

TABLE 2.—*Results of Lumbar Puncture*

Date	Initial Pressure, Mm. of Water	Color	Clot	White Blood Cells per Cu. Mm.	Red Blood Cells per Cu. Mm.	Pandy Test	Total Protein, Mg.	Sugar, Mg.	Culture
2/10	90	Blood-tinged	0	4,000	5,000	+	153	74	No growth
2/11	80	Blood-tinged	0	3,500	16,250	+	174		
2/12	100	Blood-tinged	0	500	4,000	+	51	120	
2/13	110	Blood-tinged	0	120	4,500	+	..	85	No growth

February 10, the chloride was 729 mg., and on February 11, 650 mg. (expressed as sodium chloride). On February 10, the Wassermann reaction was negative. On February 11, the urine was negative. The hemoglobin was 75 per cent (Tallqvist); the red blood cells numbered 3,380,000; the white blood cells, 15,950. A differential count showed: 82 neutrophils, 16 lymphocytes, 1 eosinophil and 1 large monocyte. There was a very slight change in the size and shape of the red blood cells. Platelets were abundant. The Kahn reaction of the blood was negative. A blood culture showed a gram-negative diplococcus. A roentgenogram of the chest showed a slight density at the base of the right lung, probably resolving pneumonia. Otherwise, the lung fields were clear. A cervical smear showed gram-negative diplococci, some intracellular. On February 12, the blood sugar was 108 mg. per hundred cubic centimeters. On February 17, the red blood cells numbered 5,401,000; the white blood cells, 26,850. A differential count showed: 82 neutrophils, 13 lymphocytes, 1 basophil and 4 large monocytes. An electrocardiogram revealed: sinoauricular tachycardia; rate, 125; P R interval, 0.14 second; Q R S 0.08 second; T_1, low; T_2 and T_3, diphasic; axis, normal. There was a high skin resistance.

Course.—The temperature, which was 102 F. on entry to the neurologic service, varied from normal to 104 F.; it averaged about 101 F. The pulse rate maintained a fairly constant level at 120. It occasionally went as low as 100 and as high as 140. The respiratory rate was usually about 45. It was as low as 30 and often as high as 50. During the first few days in the ward, the patient seemed to show considerable improvement. She became more alert, but her aphasia con-

tinued. The hemiplegic side remained largely flaccid for the first two days and then began to become spastic. No return of function took place. The gram-negative diplococcus which was grown from the blood stream was found to agglutinate with both antimeningococcus and antigonococcus serums. Sugar fermentation tests were carried out, but owing to technical difficulties a report was not received for some time. However, it was thought advisable to give the patient antimeningococcus serum, since the organism in her blood was agglutinated by the serum in spite of the fact that it probably was a gonococcus.

The patient's respiratory difficulty began to increase, and the signs of bronchopneumonia seemed to be spreading to the left side as well as to the right. On February 18, the patient was given antimeningococcus serum, after a skin test was performed and found to be negative. Only 7 cc. could be introduced into the vein; 30 cc. was given intramuscularly. At the time of the injection, the patient's

Fig. 1.—Vegetation on the anterior cusp of the aortic valve.

respiratory difficulty was becoming extreme. Half an hour later acute pulmonary edema developed. Her lungs rapidly filled; her respirations became extremely labored, and blood-streaked froth appeared at her mouth. Epinephrine, atropine and morphine were given without any improvement. The patient became rapidly worse and died about an hour after the serum was given. Artificial respiration was of no avail.

Clinical Diagnosis.—The diagnosis was gonococcal sepsis; endocervicitis; endocarditis with involvement of the aortic valve; embolus to the left internal capsule of the brain; resolving pneumonia of the lower lobe of the right lung; acute terminal pulmonary edema.

Necropsy Report.—Necropsy was performed on February 18, eighteen hours post mortem.

External Description: There exuded from the mouth a thin, brownish fluid. The abdomen was slightly distended.

Two hundred cubic centimeters of straw-colored fluid was found in the peritoneal cavity, chiefly in the pelvic portion. The stomach showed marked distention

and extended to within 2 cm. of the umbilicus. The edge of the liver was 8 cm. below the xiphoid and 3 cm. below the right costal border in the midclavicular line.

Both pleural cavities contained about 300 cc. of straw-colored fluid. There were fine fibrous adhesions throughout both cavities.

The heart weighed 320 Gm. It was normal in size. The epicardium was smooth and glistening. The myocardium was pale red and flabby; there was no gross evidence of fibrosis. On the anterior cusp of the aortic valve was found a soft, friable, grayish-yellow, rounded vegetation 1.6 cm. in diameter, partially obstructing the opening of the right coronary artery. The right and left posterior cusps of this same valve were smooth and of normal thickness. The other valves and the endocardium were normal. The coronary arteries were normal.

In both lungs there was diminution in crepitus, with a large area of consolidation in the lower lobe on either side. Section through the consolidated portions showed a grayish cut surface from which pus exuded on pressure. The cut surface of the remaining pulmonary tissue was grayish red and moist. Over the mucosa of both bronchi there was exudate.

The spleen weighed 390 Gm., and it was several times the normal size. The organ was soft, and the capsule was moderately tense. The surface showed numerous pale yellow, poorly demarcated areas of infarction varying from 1 to 4 mm. in diameter. The cut surface of the uninfarcted areas was purplish red. The pulp was extremely soft in consistence.

The stomach was dilated. When it was opened, it was found to contain from 300 to 400 cc. of light greenish fluid; the mucosa was normal.

The pancreas was normal.

The liver weighed 1,640 Gm. and was normal in size. The surface was smooth and yellowish red. The consistence was firm. Multiple sections revealed no gross pathologic changes other than congestive mottling. The gallbladder and bile ducts were normal.

The kidneys weighed 260 Gm. Both organs were slightly smaller than normal. Externally, they were grayish red. On section, the parenchyma showed prominent dark red pyramids and a well demarcated grayish-red cortex slightly thicker than normal. The capsule stripped easily and left a smooth external surface. The pelves and ureters were normal.

The suprarenal glands were normal.

The bladder was contracted. The mucosa was thickened and grayish red. Over the surface there was a greenish, creamy exudate. The urethra was opened from the external orifice inward and was found to be mildly injected and to contain a thin exudate.

The cervix showed mild lacerations. It measured 2 cm. across. The mucosa of the endocervix was dark red and was covered with a sanguineous, mucoid exudate. The endometrium was thickened and dark red. The uterus was slightly larger than normal, but otherwise was normal. The tubes were essentially normal in size. On the right, the fimbriated end of the tube was attached by delicate adhesions to the surface of the ovary.

The aorta was normal.

The brain weighed 1,310 Gm. There were much edema and congestion, and the meninges were opalescent. Section showed an area of softening on the left, extending the entire length of the external capsule and involving the external capsule and the putamen. This area was yellowish brown and necrotic, and was about 2 cm. in diameter. It did not extend to the surface or into the ventricle.

Anatomic Diagnoses: These were: acute vegetative endocarditis of the aortic valve; infarcts of the spleen; encephalomalacia; cystitis; moderate chronic endocervicitis; bronchopneumonia; pleural effusion.

Microscopic Examination: There was edema of the heart. There was infiltration of the stroma, with a few lymphocytes and large mononuclear leukocytes.

Many of the alveoli of the lungs were distended and contained fibrin, serum and large mononuclears; a few had in addition red blood cells and a sparse number of polymorphonuclear leukocytes. Early organization was seen in a few areas. The alveolar capillaries were engorged.

Immediately beneath the capsule of the spleen there was an area of necrosis surrounded by hemorrhage. The blood sinuses were markedly distended. The pulp contained many polymorphonuclear leukocytes, plasma cells, large mononuclears and lymphocytes.

The sinusoids of the liver were distended and filled with polymorphonuclear leukocytes.

There was edema of the stroma of the pancreas.

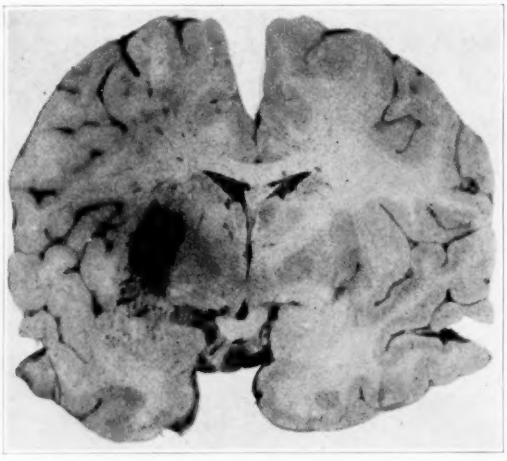

Fig. 2.—Area of softening in the left external capsule and putamen.

The renal glomeruli were distended and congested and contained polymorphonuclear leukocytes and large mononuclears; there was slight cellular proliferation of the tufts. The tubules showed desquamation of the epithelium; the lumens were filled with desquamated material; some contained serum. There were a few small focal areas of lymphocytes.

The suprarenal glands were normal.

One area of the aorta showed an accumulation of fatty, large mononuclears immediately beneath the intima.

The ovary and the tubes were normal.

There were congestion and edema of the uterine wall. Many of the blood vessels were thrombosed.

There were lymphocytic infiltration and edema of the cervix. There was slight cystic dilatation.

Sections of the area of softening of the brain showed necrosis. There was congestion of the blood vessels, with perivascular infiltration of polymorphonuclear leukocytes, plasma cells and large mononuclears. The section with the meninges

attached showed slight infiltration of the meninges, with polymorphonuclear leukocytes, plasma cells and large mononuclears.

Microscopic Diagnoses (in addition to the gross diagnoses): These were: bronchopneumonia with a small amount of organization; mild acute intracapillary glomerulonephritis; no evidence of salpingitis.

Bacteriology.—From the antemortem blood cultures a gram-negative, biscuit-shaped diplococcus was obtained. This organism was successfully cultured and passed to dextrose and maltose, from which a fermentation reaction characteristic of gonococci was obtained. At the time of autopsy, smears were taken from the heart valve, urethra, endocervix, fallopian tubes and the area of encephalomalacia. An organism identical in morphology to that obtained from the antemortem blood cultures was obtained from the heart valve and endocervix. The urethra showed a gram-negative diplococcus which was in every case extracellular, scattered among a wide variety of contaminating organisms. The smear from the endocervix showed a fair number of intracellular, gram-negative diplococci scattered among the usual saprophytic flora.

Cultures were made from all of the aforementioned regions; in addition, the blood from the heart was cultured. Pure cultures were obtained from the aortic valve and from the blood. The culture from the endocervix showed an overgrowth of contaminating flora. Smears made from this culture showed a gram-negative, biscuit-shaped diplococcus, but culturally its isolation was not accomplished, and no conclusion could definitely be made as to its identity. The cultures from the brain and fallopian tubes were not productive of growth. The following information is with reference to the organism obtained from the vegetation and from the blood from the heart.

Morphology and Cultural Characteristics: The organism was a gram-negative diplococcus, varying in size and in intensity of staining reaction, dilute carbol fuchsin being used as a counterstain in Gram's method.

Growth was readily obtained on sheep's blood beef infusion agar and ascitic fluid agar. The organism would grow but scantily on Loeffler's serum medium or in blood serum broth. No growth took place in beef infusion broth or on plain agar.

Twenty hours' incubation gave growth, but the best cultural definition came at the end of forty-eight hours. The colonies were small, discrete, round, colorless, moist, glistening, elevated, nonhemolytic and nonpigment producing.

Fermentation Reactions: Conclusive reactions were obtained in forty-eight hours with hormone broth with 1 per cent dextrose and 1 per cent maltose enriched with ascitic fluid. Reactions were complete at seventy-two hours. Control tubes were inoculated with known cultures of meningococci and gonococci. Uninoculated tubes corresponding to the foregoing and containing phenol red as an indicator were also incubated to preclude the possibility of contamination. At the end of twenty-four hours no change was observed in the tube containing the unknown organism, but in forty-eight hours its reaction was the same as that for the known gonococcus, attacking only the dextrose (table 3).

Agglutination Reactions.[1]—Agglutination Reactions with Polyvalent Antigonococcic Serum: Faintly turbid suspensions of twenty-four hour ascitic fluid agar

1. All serums used in these experiments—the polyvalent antimeningococcic, the normal horse serum and the four known types of meningococci—were obtained from the Commonwealth of Massachusetts Antitoxin and Vaccine Laboratory. The types of meningococci were: type I, no. 123; type II, no. 55; type III, no. 57; type IV, no. 60 (United States Hygienic Laboratory).

cultures of the unknown organism, of a known gonococcus grown on ascitic fluid agar and of four types of meningococci grown on ascitic fluid agar were made in salt solution and kept at 56 C. for one hour. One half of a cubic centimeter of the bacterial suspensions was added to 0.5 cc. of graded dilutions of standard polyvalent antigonococcic serum. For controls, tubes of normal horse serum and bacterial suspensions and tubes of saline and bacterial suspensions were used. The tubes were kept at 55 C. for twenty-four hours, at the end of which time readings were made.

The unknown organism was identical in its agglutination reactions with the known gonococcus, the latter showing complete agglutinations from 1:200 to 1:800 and partial up to 1:1,600. Only in a dilution of 1:200 was even partial agglutinaiton observed with three of the types of meningococci. Type IV showed no agglutination at all (table 4).

TABLE 3.—*Fermentation Reactions*

Organism	Dextrose	Maltose
Known meningococcus type I	+	+
Known gonococcus	+	—
Unknown	+	—
Tube uninoculated	—	—

TABLE 4.—*Agglutination Reactions with Antigonococcic Serum*

Strain	Final Dilutions of Antigonococcic Serum						Normal Horse Serum	Partial Agglutination	Complete Agglutination
	1:200	1:400	1:800	1:1,600	1:3,200	Saline			
Unknown organism	4	4	4	2	0	0	0	1:1,600	1:800
Known gonococcus	4*	4	4	2	0	0	0	1:1,600	1:800
Meningococcus type I	1	0	0	0	0	0	0	1:200	0
Meningococcus type II	1	0	0	0	0	0	0	1:200	0
Meningococcus type III	2	0	0	0	0	0	0	1:200	0
Meningococcus type IV	0	0	0	0	0	0	0	0	0

* Degree of agglutination reaction: 4 = comp'ete.

Agglutination Reactions with Polyvalent Antimeningococcic Serum: Employing the same technic, polyvalent antimeningococcic serum was substituted for polyvalent antigonococcic serum. In this instance only a faint, partial agglutination of the known gonococcus and of the unknown organism was observed and this in a dilution of 1:200. Three types of meningococci were completely agglutinated in dilutions of 1:200 and 1:400, and partially agglutinated in dilutions of 1:800 and 1:1,600. Type IV meningococcus was partially agglutinated only, and at a dilution of 1:200 and 1:400. These results are shown in table 5.

We thought that tables 4 and 5 presented definite evidence for the identification of the unknown organism as a gonococcus so far as the antigonococcic serum agglutinated (completely) the known gonococcus and the unknown organism in dilutions as high as 1:800 and agglutinated the meningococci only partially, and did this at a dilution of 1:200; also, since the antimeningococcic serum gave only a partial agglutination for the known gonococcus and the unknown organism, and did this in a dilution of 1:200. While the antimeningococcic serum partially agglutinated only the type IV meningococcus (table 4), this occurred in dilutions of 1:200 and 1:400, and this same type IV meningococcus was not agglutinated at all by the antigonococcic serum.

The following procedures were therefore carried through to supply additional evidence:

Precipitin Reactions.—The organism was grown for twenty-four hours on ascitic fluid agar. Each slant was washed with 3 cc. of sterile water and shaken well. The contents of the tubes were then pooled and an amount of phenol added to give a final concentration of 0.5 per cent. The material was kept at room temperature for one week and shaken daily for a period of ten minutes. The suspension was then centrifugated at high speed for one-half hour; the water-clear supernatant fluid was pipetted off and used as antigen for this test and for the complement fixation test. The precipitating serum was standard antigonococcic serum. A good precipitin ring was obtained with an antigen dilution as high as 1:800. Normal horse serum was used in place of the antigonococcic serum and saline in place of the antigen, with negative results. In the same manner, an

TABLE 5.—*Agglutination Reactions with Antimeningococcic Serum*

Strain	Final Dilutions of Antimeningococcic Serum						Normal Horse Serum	Partial Agglutination	Complete Agglutination
	1:200	1:400	1:800	1:1,600	1:3,200	Saline			
Unknown organism.....	1	0	0	0	0	0	0	1:200	0
Known gonococcus.....	1	0	0	0	0	0	0	1:200	0
Meningococcus type I....	4	4	3	1	0	0	0	1:1,600	1:400
Meningococcus type II...	4	4	3	1	0	0	0	1:1,600	1:400
Meningococcus type III..	4	4	3	1	0	0	0	1:1,600	1:400
Meningococcus type IV..	2	1	0	0	0	0	0	1:400	0

TABLE 6.—*Precipitin Reactions*

	Antigen Dilutions				
	1:200	1:400	1:800	1:1,600	1:3,200
Antigonococcic serum.....	4	3	2	—	—
Antimeningococcic serum.....	—	—	—	—	—
Horse serum.....	—	—	—	—	—

antigen was made from cultures of meningococci. No precipitin rings were formed (table 6).

Complement Fixation.—Antigen was prepared as explained. Inactivated antigonococcic serum was used as amboceptor. Two full units of complement were used throughout. Two amounts of antigen were used: 0.1 and 0.05 cc. One tenth of a cubic centimeter of antigen fixed the complement to the point where 0.002 cc. of antiserum was used. Five hundredths of a cubic centimeter of antigen fixed the complement to a point where 0.005 cc. of antiserum was used. There was no fixation when normal horse serum or antimeningococcic serum was used in place of antigonococcic serum.

COMMENT

The case proved of interest from three points of view: (1) obstetric, (2) neurologic and (3) medical.

1. From the obstetric point of view, it may be noted that the patient gave evidence of infection of the upper respiratory tract ten days ante

partum. Three days after delivery cough developed, which became productive of a grayish mucoid material and later frankly bloody; the temperature was 101 F. Presumably, bronchopneumonia had developed. The course of the penumonia was rather mild, and it began to subside a week after the onset. At this time, however, the patient's pulse rate rose to 140, and the temperature continued high. Two days later chills and hemiplegia developed. It was at this time that the first definite evidence of endocarditis was found.

Wertheim, quoted by Faure-Beaulieu, demonstrated the gonococcus in the pelvic veins with or without thrombosis. It would, therefore, appear that pregnancy and parturition would predispose to extension of the bacterial invasion. Indeed, there are two other cases of gonococcus endocarditis appearing directly after parturition in the literature, Klein's and Huebschmann's. Huebschmann's case is almost identical with ours, even to the hemiplegia. Because of this relationship to parturition, the importance of antepartum treatment of gonorrhea is evident.

2. From a neurologic point of view, the case was of interest from the first as the patient showed a complete hemiplegia associated with an infection, cause unknown. The patient did not have a stiff neck or Kernig sign, but the spinal fluid was blood-tinged and had 4,000 white blood cells per cubic millimeter. Meningitis was, of course, suspected, but smears and cultures showed no organisms, and the sugar determination was normal (74 mg. per hundred cubic centimeters). At this point no serum was given because it was felt that the cells represented an aseptic meningeal reaction to an embolus close to the ventricular wall. Later when blood cultures showed a gram-negative organism agglutinated by both antimeningococcus and antigonococcus serum, antimeningococcus serum was given intravenously and intramuscularly. Although bacterial meningitis was reasonably ruled out in this case, gonococcus meningitis does occur. Lorentz reported three cases of gonococcus meningitis with good bacteriologic evidence. On the other hand, meningococcus endocarditis may occur without meningitis (Haase and Lorentz). At the time of the patient's death, the identity of the organism had not yet been fully determined.

3. From a medical standpoint, the case was interesting because of the rarity of gonococcus endocarditis. Blake, quoted by Tebbutt, is of the opinion that temporary gonococcemia undoubtedly occurs in local gonococcus infection, characterized by arthritis and synovitis. This was demonstrated in a case report by Richard C. Cabot, in which after repeated negative blood cultures a positive culture for gonococcus was obtained when the patient had a sharp rise in temperature during arthritis. The patient recovered without clinical evidence of heart disease. Bruusgaard and Thjötta reported the case of a man with purpura,

arthritis and petechiae, in which the gonococcus was cultured from the blood, purulent spinal fluid and petechiae. There was no evidence of heart disease, and this patient also recovered. Other cases of gonococcus septicemia, without cardiac involvement and with recovery, have been reported by Jenkins.

When involvement of the endocardium occurs, however, the issue is grave. Thayer reported cases in which a doubtful diagnosis was made and recovery resulted, and Perry recently reported a case (table 1) in which recovery resulted. The valve usually attacked is the aortic, although the mitral and pulmonic are sometimes involved. Complete destruction of the aortic valve has occurred (Huebschmann). Four cases of aortic aneurysms due to the gonococcus have been reported (Thayer, 1922, and Lindau).

No treatment has been of any proved value. In Perry's case, numerous transfusions were given, as well as serum from a patient who had recently recovered from gonococcus arthritis. Antigonococcus serum has been tried (O'Brien and Bancker and Aubertin and Gambillard). In our case the results of antimeningococcus serum could not be properly evaluated.

SUMMARY

1. Forty-eight cases of gonococcus endocarditis reported in the literature since 1912 are reviewed in tabular form with respect to the evidence on which the diagnosis was made.

2. A case of gonococcus endocarditis is reported in detail. The diagnosis of acute vegetative endocarditis was made clinically and was proved at autopsy. The organism grown from the blood stream and from the vegetation on the aortic valve post mortem was identified as a gonococcus by its morphologic and cultural characteristics, fermentation reactions, agglutination, precipitin and complement fixation reactions.

3. The case is discussed from an obstetric, neurologic and general medical point of view.

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FACTORS CAUSING CLINICAL JAUNDICE IN HEART DISEASE

M. A. KUGEL, M.D.
AND
S. S. LICHTMAN, M.D.
NEW YORK

The occurrence of jaundice in cases of heart failure was first attributed to mechanical pressure of the blood stasis in the liver. This supposition has been supplanted recently by the theory advocated by Rich and his co-workers [1] that jaundice in these cases is the result of anoxemia of the liver cells. The chief support for the hypothesis of anoxemia lies in the experimental observations of Binger, Brow and Branch [2] that pulmonary infarction is attended by anoxemia and in the numerous clinical observations [3] that jaundice often supervenes on pulmonary infarction. According to Rich and his co-workers, the retention of bile pigment in the blood which occurs in practically every case of outspoken passive congestion of the liver is caused by two factors, impairment of the excretory function of the liver by anoxemia and the increased burden placed on the functionally impaired liver by the demand for the excretion of a larger amount of bile pigment than normally.

While this theory adequately explains the occurrence of latent icterus in heart disease, we believe that additional factors are required to produce frank jaundice. For example, it is not clear why one patient with congestive heart failure exhibits jaundice while in another case of apparently identical or even greater severity only latent icterus develops. In order to evaluate the relative importance of the various factors involved in the pathogenesis of frank jaundice, an analysis of clinical

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From the Laboratories of the Mount Sinai Hospital and the Medical Division, service of Dr. George Baehr.

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and pathologic material was undertaken. The following aspects of the problem were studied:

1. The significance of pulmonary infarction in the causation of clinical jaundice both in cardiac and in noncardiac disease.

2. The relationship of the duration, the degree and the type of heart failure to the incidence of clinical jaundice.

3. The rôle played by functional and anatomic disturbances of the liver.

4. The effect of disturbed renal function.

5. The significance of quantitative factors in the formation, resorption and excretion of bilirubin as influenced by pulmonic and hepatic factors.

6. The rôle played by infection, systemic or local.

In this investigation, a series of 3,000 consecutive necropsies performed between 1926 and 1931 under the direction of Dr. Paul Klemperer were studied. From this group only those patients who died primarily of cardiac disease were selected. Cases in which the cardiac disease was merely incidental to conditions such as neoplasms, peritonitis and lobar pneumonia were not included. A total of 424 cases of primary heart disease were selected.

The association of exophthalmic goiter, diabetes mellitus and other diseases which may affect the function of the liver [4] was noted. In all cases, careful attention was given to the examination of the gallbladder and bile passages in order to exclude the possibility of a mechanical obstructive jaundice.

A classification of the varieties of heart disease is shown in table 1.

SIGNIFICANCE OF PULMONARY INFARCTION

Incidence of Pulmonary Infarction in Heart Disease.—Pulmonary infarction is a common complication of heart disease, particularly in congestive failure of long standing associated with mitral and tricuspid valvular disease and with auricular fibrillation. In tabulating the incidence of infarction in the various forms of heart disease (table 1), care was exercised to select only genuine infarcts. Of the 424 cases of heart disease in the series, 151, or approximately 35 per cent, were complicated by pulmonary infarction.

As is apparent from table 1 chronic rheumatic cardiovalvular disease was most frequently complicated by pulmonary infarction (almost 50 per cent), and coronary thrombosis next, with 35 per cent; bacterial endocarditis presented the lowest incidence (20 per cent).

4. Meyer, E. L.: Function of the Liver in Diabetes Mellitus, Arch. Int. Med. **47**:182 (Feb.) 1931. Lichtman, S. S.: Liver Function in Hyperthyroidism, ibid. **50**:721 (Nov.) 1932.

Frequency of Frank Jaundice with Pulmonary Infarction.—Frank jaundice occurred in only 17 cases, or about 4 per cent of the entire series and 10.5 per cent of the cases with pulmonary infarction. In Jolliffe's [5] clinical series of 231 cases of congestive heart failure, the incidence was 2.1 per cent. Of the 17 cases of frank jaundice in our series 16 were associated with hemorrhagic infarction of the lung. Eleven of these 16 patients had rheumatic cardiovalvular disease.

Rarity of Frank Jaundice in Heart Failure without Pulmonary Infarction.—The occurrence of frank jaundice in cases of myocardial failure without pulmonary infarction is extremely rare. In 273 cases of congestive heart failure not complicated by pulmonary infarction, frank jaundice occurred only once, an incidence of 0.36 per cent. In this instance acute rheumatic fever was complicated by a large pericardial

TABLE 1.—*Incidence of Clinical Jaundice and Its Relation to Pulmonary Infarction in the Various Types of Heart Disease*

Type of Heart Disease	Total Number of Cases	Without Pulmonary Infarction		With Pulmonary Infarction	
		Number of Cases	Cases with Jaundice	Number of Cases	Cases with Jaundice
Rheumatic with valvular defects	165	88	1	77	11
Coronary artery thrombosis	95	65	0	33	2
Endocarditis, bacterial	53	42	0	11	1
Heart failure, right*	43	33	0	10	0
Syphilitic	32	24	0	8	1
Miscellaneous	36	12	0	12	1
Total	424†	273	1	151	16

* The group of cases listed under the heading of right heart failure are those due to chronic pulmonary disease, kyphoscoliosis, etc.

† The incidence of frank jaundice in cases of pulmonary infarction was 10.6 per cent, and in cases without pulmonary infarction only 0.3 per cent.

effusion compressing both lungs and acute gastritis and duodenitis as well as by acute inflammatory lesions of the coronary arteries, aorta, pulmonary artery and veins of the liver.

Absence of Frank Jaundice in Pulmonary Infarction of Noncardiac Diseases.—Thirty cases of pulmonary infarction were noted at necropsy in subjects without heart disease. In the main the infarcts were embolic in origin, complicating surgical procedures, malignant disease or peripheral infections. In no instance was clinical jaundice observed. In 9 cases the infarcts were necrotic or infected. Pleuritis complicated 2 cases and bronchopneumonia 2 others. Passive congestion of the liver was present in 9 cases. Evidence of central atrophy or necrosis was observed in 6 cases. These observations indicate that pulmonary infarction alone does not cause clinical jaundice.

5. Jolliffe, N.: Liver Function in Congestive Heart Failure, J. Clin. Investigation **8**:419, 1930.

Significance of the Size, Number, Location and Age of Pulmonary Infarcts.—There does not appear to be any difference in these factors in the 16 patients with jaundice and the 134 nonjaundiced subjects with pulmonary infarction. In 5 cases of marked jaundice a solitary infarct in the lower lobe of the right lung was present. Multiple infarcts of the lung were present in the remaining 11 cases (70 per cent).

In the 134 cases without clinical jaundice, the number of solitary and of multiple infarcts was as follows:

	Solitary Infarcts		Multiple Infarcts
	No. Cases	Lobe	
Rheumatic cardiovalvular diseases (65 cases)	11	RLL	42
	5	LLL	
	4	RML	
	2	RUL	
	2	LUL	
Coronary thrombosis (31 cases)	5	RLL	22
	3	LLL	
	1	RUL	
Right heart failure (10 cases)	2	LLL	5
	1	RLL	
	1	RUL	
	1	LUL	
Bacterial endocarditis (10 cases)	5	LLL	5
Syphilitic heart disease (7 cases)	2	RLL	5
Miscellaneous group (11 cases)	2	RUL	6
	1	RLL	
	1	LLL	
	1	LUL	

Eighty-five patients, or 63 per cent, had multiple infarctions in comparison with 70 per cent in the group with jaundice. Solitary infarcts occurred in the right lung in 37 per cent, as compared to 30 per cent in the patients with jaundice. There was a definitely greater frequency of infarction in the right lung. No difference in the size of the infarcts could be discerned in jaundiced as contrasted with nonjaundiced subjects. Old infarcts were present too infrequently (5 times in the entire series) to be of significance.

Infection of Infarcts.—Infection of infarcts occurred in 7 per cent of 135 cases without jaundice as compared to 25 per cent of 17 cases with jaundice. A complicating infection may therefore play a contributory rôle in the production of jaundice.

CONGESTIVE HEART FAILURE AS A FACTOR IN THE INCIDENCE OF CLINICAL JAUNDICE

An analysis of our data as to the duration and the type of heart failure indicates that this factor is of prime importance in the causation of clinical jaundice in cardiac disease. In estimating the onset and

degree of heart failure, definite criteria were adopted to render the data reliable. Orthopnea, dependent edema, ascites and hydrothorax in the clinical history were accepted as evidence of the existence of congestive heart failure.

Degree of Heart Failure.—No difference in the degree of the heart failure during the last illness was noted in those patients who were jaundiced and those who were not.

Duration of Heart Failure.—The duration of heart failure was classified as (1) acute or recent (less than a week), (2) less than four months and (3) more than four months.

In patients with rheumatic cardiovalvular disease the duration of the heart failure seemed to be the most important determining factor. Among those without jaundice 40 per cent suffered from acute heart failure, 54 per cent had shown failure less than four months, and 6 per cent for more than four months. In contrast, no patient with cardiac jaundice had died in acute heart failure, 46 per cent had suffered from circulatory failure for less than four months, and 54 per cent for more than four months.

Sixty-four per cent of the patients with heart failure uncomplicated by pulmonary infarction had died of acute heart failure; 30 per cent had suffered from heart failure for less than four months and 6 per cent for more than four months. The highest incidence of acute failure occurred in patients with coronary thrombosis and bacterial endocarditis (80 and 81 per cent respectively), the groups which presented the lowest incidence of jaundice and pulmonary infarction.

It is evident from these observations that the duration of congestive heart failure and of pulmonary congestion is a decisive factor in determing whether frank jaundice will develop, especially in cases of rheumatic cardiovalvular disease.

Type of Heart Failure.—Among 43 cases of primary failure of the right side of the heart due to chronic pleuropulmonary disease, kyphoscoliosis and similar conditions there was not a single instance of clinical jaundice despite the fact that the duration of heart failure corresponded closely to that in the cases of rheumatic cardiovalvular disease. In this group, pulmonary infarction was relatively infrequent. The degree and duration of congestion in the pulmonary circulation may therefore be an important element in the causation of jaundice, as well as of pulmonary infarction, in heart disease.

An analysis of the cases of coronary thrombosis (95 cases) lends support to this deduction. In the 2 instances in which jaundice was observed in coronary thrombosis, long-standing previous injury of the anterior descending branch of the left coronary artery (at least six months) had existed before the final occurrence of the recent thrombosis which caused the terminal heart failure. In both cases, chronic

passive congestion of the lungs was present. In 4 cases of coronary thrombosis complicated by pulmonary infarction and long-standing heart failure, jaundice did not develop. In 2 cases with thrombosis of the right coronary artery alone, and in 7 others accompanied by closure of the left coronary artery and pulmonary infarction, clinical jaundice did not occur. These facts speak against the importance of acute and chronic passive congestion of the liver, per se, as the essential cause of jaundice in heart disease.

RELATION OF PATHOLOGIC ALTERATION IN THE STRUCTURE OF THE LIVER TO CARDIAC JAUNDICE

Oertel[6] was the first to note "noninflammatory necroses" of the liver in cases of clinical jaundice and cyanosis. Pulmonary infarctions were present in his cases but were not stressed by him. More recently the pathogenesis of the pericentral lesions of the liver lobule have been more definitely defined.[7]

We have compared the anatomic alterations in the liver in various types of heart disease with and without pulmonary infarction and with and without jaundice. These hepatic lesions were classified as (1) chronic passive congestion, (2) pericentral atrophy or fibrosis, (3) pericentral necrosis, (4) inflammatory lesions and (5) cirrhosis of the liver.

Anatomic damage to the liver was found in all of the 17 jaundiced patients. In 3, chronic hyperemia was the sole lesion. Hyperemia was combined with pericentral atrophy or fibrosis and necrosis in 10 cases. Pericentral atrophy alone was present in 3 cases. One patient had what might be characterized as a true cardiac cirrhosis. Three had marked hemorrhages in the hepatic parenchyma. In another case a diffuse endophlebitis, possibly on a rheumatic basis, was present without atrophy or necrosis of the central lobule. A classification of the lesions and their relationship to the presence or absence of jaundice or of pulmonary infarction is presented in table 2.

Of 127 cases with pulmonary infarction but without jaundice, the liver was normal microscopically in 6 (5 per cent). Thirty-six cases (27 per cent) showed chronic passive congestion alone. Sixty-two cases (50 per cent) presented congestion and also central atrophy and necrosis. Twenty-three cases (18 per cent) showed central atrophy alone. A case of subacute bacterial endocarditis showed only focal round cell infiltrations. A case of coronary thrombosis showed a fatty liver.

6. Oertel, H.: A Further Contribution to the Knowledge of Multiple Non-Inflammatory Necrosis of the Liver with Jaundice (Hepar Necroticum cum Ictero) J. Exper. Med. **8**:103, 1906.

7. Zimmerman, H. M., and Hillsman, J. A.: Chronic Passive Congestion of the Liver, Arch. Path. **9**:1154 (June) 1930.

A significant difference in the distribution of anatomic lesions between the jaundiced and the nonjaundiced groups with pulmonary infarction is noted in the the greater incidence of combined lesions of chronic passive congestion, central atrophy and necrosis in the former group. Eighty-three per cent of the jaundiced group presented the combined lesions of chronic passive congestion, central atrophy and necrosis,

TABLE 2.—*Relative Incidence of Anatomic Lesions in the Liver in Various Types of Heart Disease*

A. Without Jaundice, with or without Pulmonary Infarction

Type of Heart Disease	Anatomic Lesions	With Infarction		No Infarcts	
		Number of Cases	Per Cent	Number of Cases	Per Cent
Rheumatic with valvular defects.	Absent	2	3	3	3
	C. P. C.*	16	25	33	44
	C. A.	11	18	12	16
	C. P. C., C. A., Nec.	34	54	28	37
Coronary artery thrombosis.....	Absent	3	10	4	9
	C. P. C.	9	29	26	57
	C. A.	4	13	6	13
	C. P. C., C. A., Nec.	15	48	10	21
Endocarditis, bacterial.....	Absent	1	10	10	30
	C. P. C.	3	30	15	45
	C. A.	3	30	4	12.5
	C. P. C., C. A., Nec.	3	30	4	12.5
Heart failure, right.....	Absent	0	0	0	0
	C. P. C.	2	25	12	52
	C. A.	1	12.5	5	22
	C. P. C., C. A., Nec.	5	62.5	6	26
Syphilitic.....	Absent	0	0	1	8
	C. P. C.	2	29	4	30
	C. A.	4	57	1	8
	C. P. C., C. A., Nec.	1	14	7	54
Miscellaneous.....	Absent	0	0	0	0
	C. P. C.	4	50	7	70
	C. A.	0	0	2	20
	C. P. C., C. A., Nec.	4	50	1	10

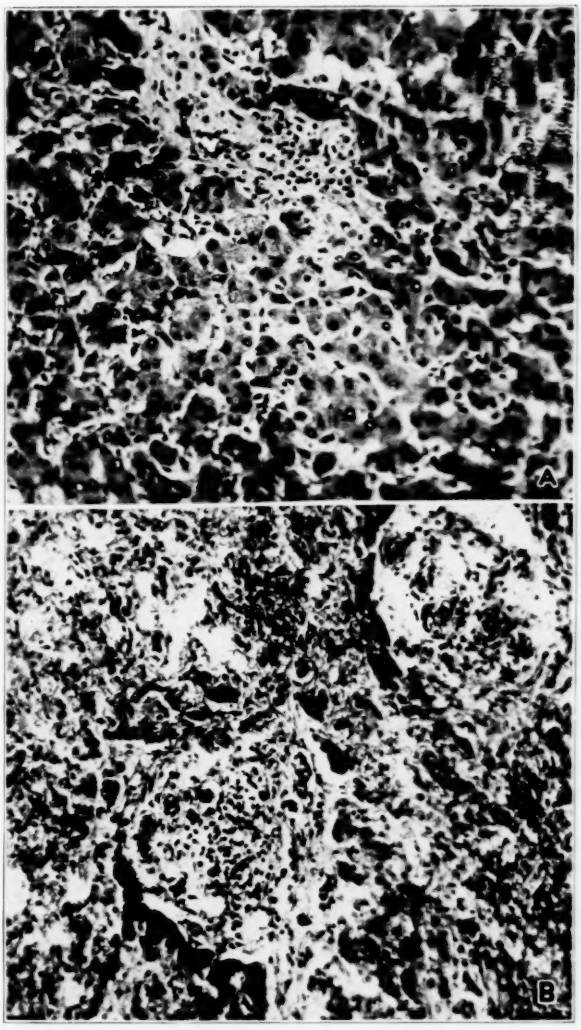
B. With Clinical Jaundice, with or without Pulmonary Infarction

Type of Heart Disease	Anatomic Lesions	With Infarction		No Infarcts	
		Number of Cases	Per Cent	Number of Cases	Per Cent
17 cases of various types of heart disease	Absent	0	..	..	..
	C. P. C.	3	18	1	..
	C. A.	3	18	..	..
	C. P. A., C. A., Nec.	10	64	..	..

* C. P. C. indicates chronic passive congestion; C. A., central atrophy; Nec., necrosis.

whereas anatomic lesions of this severity were present in only 43 per cent of the total series of cases of heart disease without jaundice.

In heart failure without pulmonary infarction (234 cases) the liver was normal in twice as many cases (9 per cent compared with 5 per cent in the cases of infarction without jaundice), and only approximately a third as many showed combined lesions of the liver (26 per cent compared with 83 per cent).



Photomicrographs showing lack of correlation between anatomic lesion in liver and intensity of clinical jaundice: *A*, section from the liver in the case with the greatest intensity of jaundice in the series (bilirubin content of blood, 8 mg. per hundred cubic centimeters; icterus index, 150). The liver shows only relatively slight changes. *B*, section from a case in which the bilirubin content was 1 mg. Note the extensive parenchymal changes as compared to those shown in *A*.

It is evident that clinical jaundice in heart disease is associated generally with marked pathologic alterations in the parenchyma of the liver. However, in individual cases one cannot predict the degree of jaundice by an examination of microscopic sections of the liver. In the case which clinically showed the most intense jaundice the anatomic changes in the liver were comparately slight, in fact less marked than in most of the cases without jaundice (fig.). It is therefore not always possible to correlate the degree of structural alteration and the functional derangement of the liver.

FUNCTION OF THE LIVER IN HEART DISEASE

A disturbance in the metabolism of blood pigment has been repeatedly demonstrated in congestive heart failure. The most constant findings are urobilinogenuria [8] and urobilinuria.[9] This has been attributed to increased destruction of blood because deposits of hemosiderin are to be seen in the lungs.[10] A test of tolerance for water and exercise has elicited urobilinuria in latent heart failure.[11] Bilirubin excretion tests, measuring the capacity of the liver to remove bilirubin administered parenterally, show a diminution of this function in heart failure.[12] A metabolic test based on the capacity of the liver to oxidize cinchophen under standardized conditions also showed altered function in cases of congestion of the liver.[13]

A thorough study of the function of the liver was recently reported by Jolliffe [5] in 16 subjects with congestive failure, some with clinical jaundice. Urobilinogen, serum bilirubin, bromsulphalein excretion and levulose tolerance tests were carried out at frequent intervals. In 93 per cent of the 16 cases some alteration in the function of the liver was noted. No characteristic type of dysfunction was found in chronic passive congestion of the liver. In only a single person were all four tests abnormal. In individual cases no parallelism between the degree of heart failure and the impairment of hepatic function could be noted. One patient suffering from most marked congestive heart failure, which ended fatally, showed no evidence of hepatic dysfunction accord-

8. Wallace, G. H., and Diamond, J. S.: The Significance of Urobilinogen in the Urine as a Test for Liver Function, Arch. Int. Med. **35**:698 (June) 1925.

9. Piersol, G. M., and Rothman, M. M.: Practical Value of Liver Function Tests, J. A. M. A. **91**:1768 (Dec. 8) 1928.

10. Fishberg, A. M.: Jaundice in Myocardial Insufficiency, J. A. M. A. **80**: 1516 (May 26) 1923.

11. Adlercreutz, E.: Urobilinuri efter vätskebelastning och kroppsrörelse vid kompenserade hjärtfel, Finska läk.- sällsk. handl. **72**:974, 1930.

12. Eilbott, W.: Funktionsprüfung der Leber mittels Bilirubinbelastung, Ztschr. f. klin. Med. **56**:529, 1927.

13. Lichtman, S. S.: Cinchophen Oxidation Test of the Function of the Hepatic Cells, Arch. Int. Med. **48**:98 (July) 1931.

ing to these tests. Fishberg [10] and Ottenberg, Rosenfeld and Goldsmith [14] observed some retention of tetrachlorphenolphthalein in the majority of cases of congestive heart disease due to faulty excretion by the liver.

Since the present study was not primarily a study of the function of the liver in heart disease, only routine observations are available. Qualitative and quantitative studies with the van den Bergh test were usually made, but bromsulphalein excretion tests and determinations of the icterus index were made in only a few instances.

Laboratory observations were made in 15 of 17 cases of cardiac jaundice. The serum bilirubin varied between 0.5 and 8 mg. per hundred cubic centimeters. In 12 of the 15 cases it exceeded 2 mg. Of 11 cases in which a qualitative van den Bergh test was made, a prompt positive result was present in 10. The remaining case gave a direct delayed reaction. Bilirubinuria was present in all the cases with jaundice. An icterus index of 110, 120 and 150 on three tests was obtained in a case which on two occasions showed a serum bilirubin content of 8 mg. per hundred cubic centimeters with a prompt positive direct van den Bergh reaction. The two cases with the highest serum bilirubin readings (8 mg. per hundred cubic centimeters) were cases of mitral stenosis and of coronary thrombosis, respectively.

In 21 instances of heart disease with pulmonary infarction but without clinical jaundice the serum bilirubin was determined. In 13 cases normal values, below 0.35 mg. per hundred cubic centimeters, were recorded. Latent icterus, the bilirubin varying between 0.6 and 2 mg., was present in the remaining 8 cases. An indirect van den Bergh reaction was present in all instances except in a case which gave a delayed direct reaction with 0.35 mg. of bilirubin.

In 2 cases of heart failure with pulmonary infarction, one with, and the other without, jaundice there was a bromsulphalein dye retention in the blood of 15 per cent in thirty minutes. A case of mitral and tricuspid insufficiency without jaundice showed a serum bilirubin of 0.6 mg. per hundred cubic centimeters and bile in the urine on two occasions. In the case in which jaundice was present the 15 per cent retention was recorded during the phase of recovery.

The icterus index was determined in 6 cases of heart disease with pulmonary infarction but without jaundice. Normal readings of 5 and 6 were obtained in 3 cases. Latent icterus, indicated by readings of 9, 12 and 15, was shown in the remaining 3 cases.

From the foregoing data, it is evident that in heart failure with jaundice the degree of retention of bilirubin in the blood may approach

14. Ottenberg, R.; Rosenfeld, S., and Goldsmith, L.: The Clinical Value of the Serum Tetrachlorphenolphthalein Test for Liver Function, Arch. Int. Med. **34**: 206 (July) 1924.

that found in obstruction of the common bile duct and the quantitative van den Bergh reaction may equal that seen in a "regurgitation" type of jaundice (Rich). Advanced degrees of heart failure may exist, however, without retention of bilirubin in the blood.

RENAL FUNCTION IN RELATION TO OCCURRENCE OF JAUNDICE IN HEART DISEASE

The occurrence of azotemia in the course of advanced heart failure is commonly observed. When circulatory stasis is superimposed on a previously damaged kidney, uremia may supervene. A reciprocal relationship between excretion of certain substances by the liver and by the kidney has been noted. In the presence of retention of bilirubin due to failure of excretion of this substance by the liver, the kidney may assume the burden of excretion. This has been noted by Hanner and Whipple [15] in studying excretion of phenolsulphonphthalein in the urine in the presence of experimental injury to the liver in dogs. Resnick and Keefer [16] made a similar experimental observation when studying the causation of jaundice in heart disease. We therefore tried to observe whether the retention of nitrogenous substances in the blood affected the incidence of clinical jaundice.

In the jaundiced group only a single case showed evidence of renal impairment as measured by a retention of urea nitrogen in the blood of 32 mg. per hundred cubic centimeters. There were 11 nonjaundiced patients in whom the urea nitrogen of the blood varied between 25 and 95 mg. per hundred cubic centimeters. The renal factor does not, therefore, appear to be significant.

FORMATION AND RESORPTION OF BILIRUBIN

It has been demonstrated repeatedly that localized extravasations of blood, spontaneous or artificially produced, rarely cause bilirubinemia despite the fact that bilirubin is formed locally.[17] For final

15. Hanner, J. P., and Whipple, G. H.: The Elimination of Phenolsulphonphthalein by the Kidney. The Influence of Pathologic Changes in the Liver, Arch. Int. Med. **48**:598 (Oct.) 1931.

16. Resnik, W. H., and Keefer, C. S.: Jaundice Following Pulmonary Infarction in Patients with Myocardial Insufficiency: II. An Experimental Study, J. Clin. Investigation **2**:389, 1926.

17. van den Bergh, A. A. H., and Snapper, I.: Untersuchungen über den Icterus, Berl. klin. Wchnschr. **51**:1180, 1924. Whipple, G. H., and Hooper, G. W.: Icterus. A Rapid Change of Hemoglobin to Bile Pigment in the Pleural and Peritoneal Cavities, J. Exper. Med. **23**:137, 1916. Rich and Resnik.[1] Ohno, Yukizo: Zur Frage der Pathogenese des Ikterus, Med. Klin. **23**:1577, 1927. Aschoff, L.: Ueber Bildungs-und-Ausscheidungsstörungen der gallenfähigen Substanzen besonders des Gallenfarbstoffs, Acta path. et microbiol. Scandinav. **5**:338, 1928. van den Bergh, A. A. H., and Snapper, I.: Ueber anhepatische Gallenfarbstoffbildung, Berl. klin. Wchnschr. **52**:1082, 1915.

acceptance of such work, it must be proved that the local extravasation of red blood cells has undergone conversion to bilirubin, and that the bilirubin has not been reduced to urobilinogen by local bacterial action or anoxemia [18] before absorption into the blood stream. The demonstration of bilirubin crystals in hematomas [19] furthermore indicates that under certain conditions this substance is insoluble. As serum is an excellent solvent of bilirubin, Ottenberg [20] has explained the eccentric distribution of jaundice in the presence of edema reported by Meakins and Page [21] on the basis of the low protein content of edema fluids.

In our opinion, local hemolysis in the lung is a factor of paramount importance. There is experimental evidence to indicate that after repeated injections of blood into the bronchial tree, hemolysis occurs instead of phagocytosis of the fragmented erythrocytes.[22] Only after repeated injections did Maugeri [23] note a significant increase in serum bilirubin. In unpublished observations Fried [24] was also able to demonstrate bilirubinemia by producing pulmonary hematomas in two dogs.

Absorption of fluids from the lungs and pleural cavity takes place rapidly. The classic studies of Nothnagel [25] and Fleiner [26] on the absorption of corpuscular elements of blood from the bronchial tree and pleural cavity indicate that the lymphatics convey the intact cells to the lymph node filters. The thoracic duct usually contained few erythrocytes. Investigation of pathologic material associated with recent antemortem hemorrhage into the lung confirmed the very rapid removal of interstitial hemorrhages. In the presence of disease of the mediastinal lymph nodes, as in tuberculosis and other chronic infections, however, obstruction to removal of corpuscular elements was evident. In such instances the resorption was delayed or prevented.

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18. Rabinowitch, I. M.: The Origin of Urobilinogen: Clinical Experiment, Arch. Int. Med. **46**:1014 (Dec.) 1930.

19. Virchow, R.: Die pathologischen Pigmente, Virchows Arch. f. path. Anat. **1**:379, 1847.

20. Ottenberg, R.: Jaundice in Heart Disease, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 3, p. 917.

21. Meakins, J.: Distribution of Jaundice in Circulatory Failure, J. Clin. Investigation **4**:135, 1927. Page, I. H.: Ipsolateral Edema and Contralateral Jaundice Associated with Hemiplegia and Cardiac Decompensation, Am. J. M. Sc. **177**:273, 1929.

22. Briscoe, J. C.: An Experimental Investigation of the Phagocytic Action of Alveolar Cells of the Lung, J. Path. & Bact. **12**:66, 1908.

23. Maugeri, S.: Die pulmonogene Entstehung des Ikterus, Beitr. z. path. Anat. u. z. allg. Path. **86**:375, 1931.

24. Fried, B. M.: Personal communication.

25. Nothnagel, H.: Zur Resorption des Blutes aus dem Bronchialbaum, Virchows Arch. f. path. Anat. **71**:414, 1877.

26. Fleiner, W.: Ueber die Resorption corpuscularer Elemente durch Lungen und Pleura, Virchows Arch. f. path. Anat. **97**:112 and 282, 1888.

A correlation of the factors of local hemolysis and increased activity of the reticulo-endothelial system furnishes, we believe, optimum conditions for the rapid formation of bilirubin. Under the optimum conditions for the solubility of this bilirubin, fluids are absorbed at a rapid rate from the lung tissue.

RÔLE OF SYSTEMIC AND LOCAL PULMONARY INFECTION

The enhanced activity of the reticulo-endothelial system which attends infection [27] may play a prominent rôle in the genesis of jaundice. For this reason we analyzed our material for the presence of infection. We depended on anatomic evidence of infection rather than on fever and leukocytosis alone.

The types of infection encountered were as follows: (1) infection and necrosis of pulmonary infarcts; (2) pleuritis, the result of exten-

TABLE 3.—*Incidence of Systemic or Pleuropulmonary Infection in Heart Disease in Relation to Pulmonary Infarction and Jaundice*

Type of Infection	Without Jaundice with Infarct (151 Cases) per Cent	With Jaundice (17 Cases) per Cent
Infection of infarct	7.0	25
Pleuritis	2.0	12
Bronchopneumonia	11.0	25
Empyema	0.0	6
Acute rheumatic fever*	31.0	50
Hemolytic streptococcemia	0.0	6
Average	8.5	20

* Incidence only in the group with rheumatic cardiovalvular disease.

sion of pulmonary infarcts to the surface of the lung; (3) empyema, the result of secondary infection of infarcts or effusions; (4) bronchopneumonia, and (5) systemic infections, such as acute rheumatic fever and hemolytic streptococcemia. A comparison of the results in the cases with and without jaundice is shown in table 3. In the cases in which jaundice was present infection in one form or another occurred more than twice as frequently (20 to 9 per cent).

SUMMARY AND CONCLUSION

Two factors, the duration and the type of myocardial failure, are mainly responsible for the occurrence of pulmonary infarction. The lowest incidence of infarction occurred in patients with subacute bacterial endocarditis, in whom congestive heart failure rarely occurs, and in those with primary failure of the right side of the heart, in whom the left side is usually competent until the end. The highest incidence occurred in the group with rheumatic cardiovalvular disease, mostly in

27. Sacks, B.: The Reticulo-Endothelial System, Physiol. Rev. **6**:504, 1926.

those with disease of the mitral valves. This group also showed a longer duration of heart failure. Long standing pulmonary congestion, therefore, is a significant factor in the causation of pulmonary infarction, confirming the early experimental observations of Karsner and Ashe.[28]

The data indicate that jaundice is not directly correlated with the degree of anoxemia induced by pulmonary infarction. If it were true that the occurrence of frank jaundice depended wholly on the existence of an advanced degree of anoxemia, a much higher incidence of jaundice would occur in the cases of multiple and massive infarctions and of lobar pneumonia. Yet the existence of a pulmonary infarct appears to be an almost indispensible factor in the causation of clinical jaundice, occurring in 94 per cent of the cases. However, a combination of circumstances and factors is necessary.

In addition to long-standing pulmonary congestion, a higher incidence of anatomic lesions of the liver and of systemic or pulmonary infection is found in the cases with jaundice. A survey of the anatomic lesions of the liver and studies of the function of the liver make it apparent, however, that unless true cardiac cirrhosis or diffuse inflammatory vascular disease of the liver exists the jaundice is not primarily hepatogenous.

Infection, systemic or pleuropulmonary, also plays an important contributory rôle, probably by influencing the rate of formation and resorption of bilirubin from its source, the pulmonary infarct, and the rate of its excretion by the liver.

These clinical and anatomic observations lead us to the following concept of the probable mechanism responsible for frank jaundice in heart failure: In a patient with long-standing pulmonary stasis due to cardiac insufficiency, pulmonary infarction occurs. From this rich source, hemoglobin is made available by destruction and hemolysis of red blood cells, and bilirubin is rapidly formed. The presence of serum in the lung, owing to congestion and often to infection, facilitates the solution and absorption of the bilirubin. The capacity of the liver to excrete this substance is impaired, owing to anoxemia and to the toxic effect of infection on the parenchyma of the liver. However, unless extensive disease of the liver, i. e. true cirrhosis, is present, the causation of the frank jaundice is primarily pulmonogenic. The deleterious effects of anoxemia and of infection on the liver cells play a necessary but only a secondary rôle. The pulmonic factors of primary importance are the duration and type of heart failure, i. e., prolonged failure of or obstruction in the left side of the heart and pulmonary congestion, and the local factors favoring the rapid formation and absorption of bilirubin, i. e., pulmonary infarction, hemolysis of erythrocytes and local or systemic infection.

28. Karsner, H. T., and Ashe, J. E.: Studies in Infarction: XI. Experimental Bland Infarction of the Lung, J. M. Research **22**:205. 1912-1913.

PREMATURE LEFT VENTRICULAR BEATS FROM ELECTRICAL STIMULATION OF EXPOSED HUMAN HEART

CLAYTON J. LUNDY, M.D.
AND
CHARLES M. BACON, M.D.
CHICAGO

The value of the study of the excitatory process in the exposed human heart by Barker, Macleod and Alexander [1] is unquestioned. Their observations on electrically induced extrasystoles are of special interest. The deflection of Q-R-S in the three leads took direction according to a semblance of an orderly manner, when considered in relation to the many points stimulated. This direction of Q-R-S in the three leads corresponds to that which is frequently observed clinically and which is not readily understood according to the classic explanation. The result is that at present extrasystoles are not accurately localized with regard to their site of origin.

The work of Barker will probably be a forerunner of a proved pattern whereby one will be able to compare the electrocardiogram of extrasystoles from a patient with those from known sources in the human heart, and to make an accurate statement as to their site of origin.

Opportunities for such studies are not frequently available. Marvin and Oughterson [2] recently confirmed a part of the original observations. We are herewith presenting further evidence, from a different part of the heart than is shown in the original observation, in a third instance of a study of the form of ventricular extrasystoles in the exposed human heart.

Through Dr. Edwin M. Miller of the Presbyterian Hospital of Chicago, we were informed of the presence of a patient, 4 years of age, at the Chicago Municipal Contagious Disease Hospital, in whom a purulent pericardial effusion developed following influenza of the upper respiratory tract. Dr. Miller had performed a pericardiotomy through the left half of the sternum at the levels of the fourth and fifth ribs.

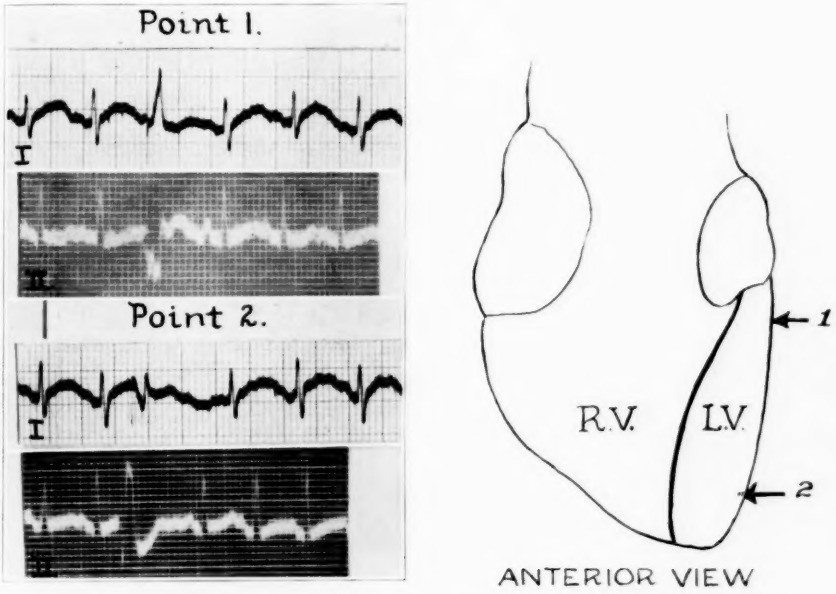
From the Department of Medicine, Rush Medical College, The University of Chicago and the Municipal Contagious Disease Hospital.

1. Barker, P. S.; Macleod, A. D., and Alexander, J.: The Excitatory Process Observed in the Exposed Human Heart, Am. Heart J. **5**:720 (Aug.) 1930.

2. Marvin, H. M., and Oughterson, A. W.: The Form of Premature Beats Resulting from Direct Stimulation of the Human Ventricles, Am. Heart J. **7**:471 (April) 1932.

Through the operative wound could be seen the left auricular appendix and the basal portion of the left side of the ventricles. With the permission of Dr. A. L. Hoyne, we were permitted to elicit electrically excited extrasystoles from this heart.

The method used was the same as that of Barker, except that we observed only leads I and III simultaneously, and we used only about 6 volts of current. Mr. F. V. Schaal, of the Cambridge Instrument Company, allowed us to use a portable electrocardiograph, and he assisted in its operation at the time of the experiments.



Results from stimulation of *points 1* and *2*. In *point 1*, leads I and III were recorded simultaneously. The main deflections are discordant: up in lead I and down in lead III. In *point 2*, leads I and III were recorded simultaneously. The main deflections are discordant: down in lead I and up in lead III. The diagram at the right is of the anterior surface of the heart. *Point 1* is at the posterior lateral margin near the base of the left ventricle. *Point 2* is near the apex on the posterior surface of the left ventricle near the posterior lateral border.

Two points were stimulated along the left border of the heart, both in the left ventricle. The first point was near the base (accompanying figure) on the lateral posterior margin. The second point was near the apex (fig.) on the posterior surface near the left lateral margin. The first point of stimulation was visible; the second was not. The intraventricular septum was located by the anterior descending branch of the left coronary artery, and, in addition, the septum was seen to

remain as a firm band between the bulging and relaxed walls of both ventricles during diastole. We believe that there is no question but that in both instances the left ventricle was stimulated.

The results are shown in the accompanying figure. In both electrocardiograms the curves are discordant. When the left ventricle was stimulated near the base, the main deflection of Q-R-S was upright in lead I and inverted in lead III. When the left ventricle was stimulated near the apex, the main deflection of Q-R-S was inverted in lead I and upright in lead III. Stimulation of other points was not done because of the condition of the patient, who died twenty-two days after these observations were made. Postmortem examination was not obtained.

COMMENT

Our curves differ in detail from those of Barker and his co-workers, because they were derived from different sites. Our basal stimulation (our point 1) was on the lateral posterior surface of the left ventricle, to the left of Barker's point 11, and the entire width of the heart posteriorly when compared with his point 1. The distance from the apex or base puts our point 1 at about the same level as Barker's points 1 and 11.

Our apical stimulation (our point 2) is in a similar location to the point B of Marvin and Oughterson's [2] observations (fig. 3, p. 474). As may be seen, the resulting electrocardiograms are similar.

Such observations as these and the works cited may result in the establishment of a chart or pattern whereby one will be able to compare extrasystoles as they occur in patients with those from known sources in the human heart, and to make an accurate statement as to their site of origin. Such observations may also shed light on the controverted question of the significance of ventricular extrasystoles and may attach prognostic importance to those from certain regions.

CONCLUSIONS

1. Electrically induced extrasystoles from the base and apex of the human left ventricle gave discordant Q-R-S complexes; the extrasystole arising from the base was upright in lead I and inverted in lead III; that arising from the apex was inverted in lead I and upright in lead III.

2. The ventricular extrasystole elicited from our point 1 is from a region heretofore unexplored.

3. The ventricular extrasystole elicited from our point 2 corresponds to and confirms one observation made by Marvin and Oughterson.

122 South Michigan Avenue.

55 East Washington Street.

INFLUENCE OF SCLEROTIC ARTERIAL WALL ON BLOOD PRESSURE MEASUREMENTS

REPORT OF CASE WITH CALCIFICATION OF ONE RADIAL ARTERY

DAVID AYMAN, M.D.
BOSTON
AND
A. KRAKOWER, M.D.
MONTREAL, CANADA

Many studies have been made to determine whether a markedly sclerotic artery requires considerably more pressure to obliterate its lumen than a normal soft artery. The results of these investigations, largely derived from studies made directly on excised arteries, support the view that the pressure of but a few more millimeters of mercury is required to obliterate the lumen of a calcified artery. These findings apparently have not been verified in the living person. A person who had a markedly sclerotic radial artery in one arm and a soft radial artery in the other arm would offer an opportunity for an answer to this question by a comparison of simultaneous readings of the blood pressure in both arms. We have recently observed such a person, and the results of studies on him are presented in this paper.

REVIEW OF THE LITERATURE

An excellent summary of the literature on this subject is presented in the papers of MacWilliam and Kesson [1] and Janeway and Park,[2] to which one should refer for details. Analysis of the literature shows that the various studies may be divided into those made on excised "dead" arteries, those made on recently excised, presumably "living" arteries and studies on living patients. In the studies made on excised dead arteries, von Basch [3] and Martin [4] found that the lumen of the

From the Medical Clinics of the New England Medical Center and Beth Israel Hospital, Boston.

1. MacWilliam, J. A., and Kesson, J. E.: The Estimation of Systolic Blood Pressure in Man, with Special Reference to the Influence of the Arterial Wall, Heart **4**:279 (May 29) 1913.

2. Janeway, T. C., and Park, E. A.: An Experimental Study of the Resistance to Compression of the Arterial Wall, Arch. Int. Med. **6**:586 (Nov.) 1910.

3. von Basch, S.: Der Sphygmomanometer und seine Verwerthung in der Praxis, Berl. klin. Wchnschr. **24**:181, 1887.

4. Martin, C. J.: The Determination of Arterial Blood Pressure in Clinical Practice, Brit. M. J. **1**:865 (April 15) 1905.

normal artery could be obliterated by a pressure of from 1 to 2 mm. of mercury, whereas a pressure of from 5 to 7 mm. was required to obliterate the lumen of calcified arteries. On the other hand, Herringham and Womack,[5] also working with excised "dead" arteries, found that a pressure of from 4 to 34 mm. of mercury was required to obliterate the lumen of calcified vessels. They found no correlation between the age of the person, the condition of the arterial wall and the pressure necessary for obliteration.

Investigations on excised "living" arteries, in general, have shown that the resistance of the vessel wall has no significant influence on the measurement of blood pressure. Janeway and Park[2] concluded that in the case of the normal large artery only a few millimeters of pressure were required for the obliteration of its lumen, and that calcified and thickened vessels were obliterated by a pressure of 20 mm. at the most, and usually of from but 10 to 15 mm. MacWilliam and Kesson[3] and MacWilliam and Melvin[6] found that relaxed living arteries with a normal or "thickened" wall offered but slight resistance to compression, usually not more than a few millimeters of mercury. Janeway and Park and MacWilliam, Kesson and Melvin showed that any artery the smooth muscle of which was contracted became extremely resistant to obliteration of its lumen by pressure, but that this state could be overcome quickly and easily by repeated compression and massage. In this way they explained the results of Herringham and Womack's studies on excised dead arteries, in which considerable pressure was required to obliterate the lumen of calcified arteries.

In addition to the foregoing studies made directly on excised arteries, observations on the living patient supply indirect evidence for the view that the uncontracted artery, whether normal or calcified, furnishes but little resistance to the obliteration of its lumen. Hensen,[7] in 1900, studied the blood pressure of a moribund patient with tuberculosis who, palpation showed, had moderate arteriosclerosis of the brachial artery. He found the systolic blood pressure as low as from 30 to 40 mm. of mercury, and therefore contended that since there was still some pressure of blood within the artery, the resistance of the arterial wall itself could not have exceeded 20 mm. of mercury. Dameshek and Loman[8] recently compared blood pressure readings as obtained by the usual

5. Herringham, W. P., and Womack, F.: Proc. Roy. Soc. Med. (Sect. Med.) **2**:37, 1908.

6. MacWilliam, J. A., and Melvin, G. S.: The Estimation of the Diastolic Blood Pressure in Man, Heart **4**:393 (June 14) 1913.

7. Hensen, H.: Beiträge zur Physiologie und Pathologie des Blutdrucks, Deutsches Arch. f. klin. Med. **67**:505 (July) 1900.

8. Dameshek, W., and Loman, J.: Direct Intra-Arterial Blood Pressure Readings in Man, Am. J. Physiol. **101**:140 (June) 1932

clinical method and by a direct intra-arterial method, and on the basis of indirect evidence they have concluded that a sclerosed artery introduces little if any error in measurements of the blood pressure. No roentgen studies of the arteries were made. Williamson[9] took into consideration the fact that arteriosclerosis is usually more marked in the lower extremities. In his studies, readings of the blood pressure were made in the arms and thighs of arteriosclerotic patients. Marked differences in the blood pressure could be demonstrated. These results cannot be interpreted satisfactorily, because the observer in this study did not determine by x-rays the condition of the arteries in his subjects, nor did he make simultaneous readings of the blood pressure in the arm and leg. Finally, Müller,[10] by direct determination of the venous pressure, indirectly concluded that the tension of the arterial wall averaged 12 mm. of mercury both in healthy adults and in patients with arteriosclerosis but without hypertension.

METHOD AND RESULTS OF PRESENT STUDY

The present study was prompted by the finding of an unusual clinical condition, namely, a markedly sclerotic and calcified radial artery in one forearm and a soft radial artery in the other arm.

P. K., a man, aged 64, entered the Observation Hospital of the New England Medical Center complaining of weakness and pallor of three years' duration. Most of his life he had done odd jobs, and he said that he had not especially used one arm more than the other for any period of time. He had been a waiter for less than a year. Examination revealed pallor of the mucous membranes and skin; a smooth, glistening tongue; absent vibratory sense in the lower extremities, and absence of free hydrochloric acid in the gastric juice after a subcutaneous injection of histamine. The hemoglobin was 56 per cent (Sahli), and the red blood count was 1,800,000 per cubic millimeter. A diagnosis of pernicious anemia, subacute combined sclerosis of the spinal cord and arteriosclerosis was made, and liver extract was given with a satisfactory response.

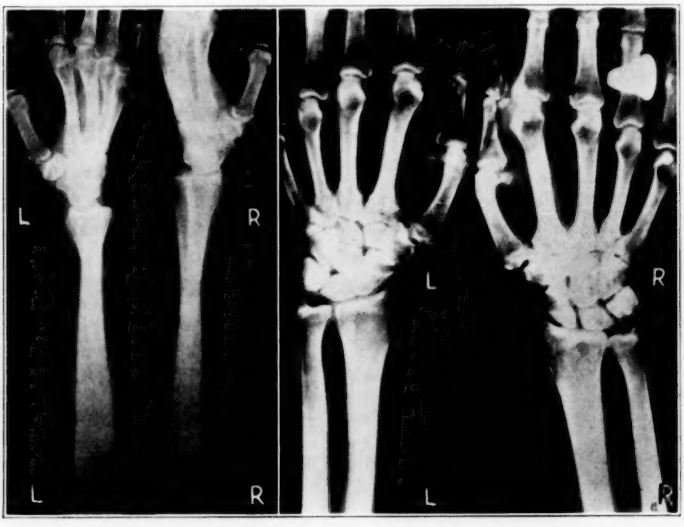
In the course of examination, it was noted that the right radial artery was markedly sclerotic and beaded and moderately tortuous. It could thus be felt over 7 cm. of its length. It was impossible to obliterate this pulse by digital compression, although the pressure of the manometer cuff on the arm or the forearm was easily able to do so. In contrast to this, the left radial artery was moderately soft, being just palpable against the radius. With compression of the brachial artery above systolic pressure, the left radial vessel could not be palpated at all. Both brachial arteries were markedly thickened on palpation, the right more than the left. The heart was of normal size clinically and radiographically. An electrocardiogram revealed no abnormality. Renal function tests were within normal limits. The blood calcium was 10.9 mg. per hundred cubic centimeters.

9. Williamson, O. K.: Clinical Observations on the Influence of the Vessel Wall on (So-Called) Arterial Blood Pressure Readings, Proc. Roy. Soc. Med. (Sect. Med.) **2**:229 (April 27) 1909.

10. Müller, A.: Ueber die klinische Bestimmung der Arterienwandspannung und ihre Bedeutung, Deutsches Arch. f. klin. Med. **146**:118 (Jan.) 1925.

Roentgenograms of the vessels of the upper extremities are shown in the accompanying figure. The widespread calcification of the vessels is easily observed, and it was found to be more marked in the lower extremities (plate not shown). Both brachial arteries were markedly calcified (plate not shown), the right more than the left. Both ulnar arteries were markedly calcified. The right radial artery likewise was calcified. A slight amount of calcification of the left radial artery could be made out at the level of the styloid process of the radius, a portion of the artery not utilized in this study. In spite of the taking of numerous other views of the left forearm in every possible position, the left radial artery could not otherwise be visualized by the x-rays.

Studies of the blood pressure were carried out in the following manner: First, readings of the blood pressure were obtained simultaneously over the brachial



Roentgenograms of the upper extremities of P. K. The right extremity is indicated by *R;* the left, by *L.*

arteries of both arms. The blood pressure cuffs were placed over both arms and connected by a T piece to a single mercury manometer. In this way, the blood pressure cuffs on both arms could be simultaneously inflated and deflated from the bulb on either arm. The patient was kept in a horizontal position, with both arms and the heart at the same level. Before making readings on both arms, both observers made simultaneous readings on one arm through a double stethoscope, in order to be certain that they used the same criteria for systolic and diastolic readings, and had the same acuteness of hearing. In making readings, the auscultatory method was used whenever possible. The first sounds heard on deflating the cuff were noted as systolic, even when they were not constant owing to respiratory variations. The beginning of the fourth phase was used as the criterion of diastolic blood pressure. In table 1, it is seen that both observers checked closely on many readings of the same side. Therefore, in simultaneous readings on both

TABLE 1.—*Simultaneous Readings of Blood Pressure of Left Brachial Artery, Made by Both Observers, Using a Double Stethoscope*

Date	Observer	Blood Pressure Readings	
		Systolic	Diastolic
3/17/32	D. A.	116	58
	A. K.	116	58
	D. A.	112	60
	A. K.	112	56
	D. A.	112	60
	A. K.	112	58
3/19/32	D. A.	120	64
	A. K.	120	64
	D. A.	132	64
	A. K.	132	64

TABLE 2.—*Simultaneous Readings of Blood Pressure on Right and Left Brachial Arteries in Patient with Sclerotic Right Radial and Soft Left Radial Artery*

Date	Right			Left		
	Observer	Systolic	Diastolic	Observer	Systolic	Diastolic
3/17/32	D. A.	118	60	A. K.	116	62
		116	64		114	60
		116	64		108	60
		116	60		108	62
	A. K.	118	64	D. A.	112	62
		112	66		110	62
		114	60		110	62
		118	66		116	62
3/19/32	D. A.	106	62	A. K.	116	64
		110	64		112	66
		112	62		114	66
	A. K.	108	64	D. A.	110	66
		112	62		114	64
		110	62		114	66
3/23/32	D. A.	130	68	A. K.	120	68
		124	70		120	68
		124	70		118	70
	A. K.	124	70	D. A.	122	70
		126	70		120	70
		122	72		122	72
		120	72		122	72
		120	72		122	70
	D. A.*	122	72	A. K.	118	68
		118	70		120	70
5/22/32	D. A.	116	80	A. K.	126	86
		148	82		140	84
		142	84		144	84
		146	84		144	84
		140	84		142	84
	D. A.	136	82	A. K.	130	78
		136	78		136	80
		132	78		128	78
		130	80		132	82
		130	88		134	88
	A. K.	132	86	D. A.	130	80
		128	76		130	80
	A. K.	130	78	D. A.	130	78
Average of all readings		124	71		122	71

* Patient sitting up with hands by sides.

arms, a leeway of 2 mm. at the most might be given to cover any possible error in reading the mercury. In table 2 are the readings made simultaneously on both arms, each observer shifting from one arm to the other after a series of two or more readings. In table 3 are the readings made over the radial vessels, with the

TABLE 3.—*Simultaneous Readings of Blood Pressure in Right and Left Radial Arteries, with Blood Pressure Cuffs on Forearms, in Patient with Sclerotic Right Radial Artery and Soft Left Radial Artery*

		Right			Left	
Date	Observer	Systolic	Diastolic	Observer	Systolic	Diastolic
3/17/32	A. K.	124	68	D. A.	118	66
		128	72		120	64
		124	76		124	68
		126	74		122	66
3/19/32	A. K.	128	*	D. A.	124	
		128			122	
		126			122	
	D. A.	124		A. K.	124	
		124			124	
	A. K.	126		D. A.	122	
		122			122	
		122			120	
3/23/32	A. K.	144		S. H. P.	134	
		142			138	
		144			144	
		132			128	
		136			136	
		136			136	
	S. H. P.	136		A. K.	128	
		138			136	
		132			136	
	D. A.	118	†	A. K.	118	
5/22/32	D. A.	150		A. K.	148	
		142			146	
		144			140	
	D. A.	140		A. K.	132	
		138			134	
	A. K.	144		D. A.	140	
		146			138	
	A. K.	144		D. A.	138	
		142			138	
Average of all readings		134			131	

* From this point all readings by palpation.
† Patient sitting up with arms by side.

blood pressure cuff over the lower part of each forearm. At first it was possible to use the auscultatory method over the radial artries, but later it was found rather difficult to hear the sounds over the calcified radial artery, so that only the palpatory systolic readings were made. In general, it is seen that the systolic blood pressure at the radial artery by palpation was usually from 2 to 8 mm. more on the right (calcified) than on the left side, although the average showed a difference of only 3 mm. It is also seen that the average of all the readings of the radial arteries was about 10 mm. higher than those of the brachial arteries.

COMMENT

Clinically and radiographically, we are dealing with a patient who has in his right forearm a markedly sclerotic radial artery over its entire length, and in his left forearm a soft and only slightly thickened radial vessel. Both of the radial arteries seem to be of the same size. If both the radials were soft and uncalcified, we would expect approximately the same readings on both sides, for we have found bilateral simultaneous readings to be approximately the same in sixteen normal people who had normal blood pressure and soft radial arteries. We also found that simultaneous bilateral readings of the blood pressure in twenty patients with arteriolar hypertension showed no appreciable differences. If sclerosis of the radial artery causes little if any increase in the pressure necessary for obliteration of its lumen, we would expect little if any increase in the blood pressure on the right side. Actually, we found that of the thirty-one simultaneous readings of the blood pressure in the radial arteries of our patient, twenty-one showed readings from 2 to 10 mm. higher on the right side, and eight showed exactly the same readings on both sides. The average of all systolic readings of the right radial was 134 mm., while on the left side it was 131 mm. The tendency to slightly higher readings on the right (sclerotic) side, however, cannot be attributed to the sclerosis, for in similar studies on sixteen normal adults, we as well as others have found that for some unexplained reason the blood pressure was often slightly higher (from 2 to 6 mm.) on the right side. Blumgart and Ernstene [11] have suggested that since the right arm is usually larger than the left arm, the arteries in the right arm are probably larger than those in the left arm. Therefore, the flow of blood through any part of an artery of the right arm meets with slightly less resistance than through the corresponding part of the left arm. The result would be a slightly higher systolic blood pressure in the right arm. This idea is in keeping with Hering's [12] findings that the blood pressure is always lower in an atrophic arm than in a normal arm. If the foregoing is true, one would expect slightly higher blood pressure readings in the left arms of left-handed people. Practically all of our patients mentioned were right-handed, so that we are unable to verify that possibility with our material. Our evidence strongly supports the view that calcification of a vessel influences little, if at all, the reading of the blood pressure.

11. Blumgart, H. L., and Ernstene, A. C.: Hemangiectatic Hypertrophy and Congenital Phlebarteriectasis, Arch. Int. Med. **49**:599 (April) 1932; personal communication to the authors.

12. Hering, E.: Ueber den Einfluss der Weichteile auf die Werte der Blutdruckmessung, Deutsches Arch. f. klin. Med. **133**:306 (Sept.) 1920.

There was one possible source of error in our study which we had to eliminate. This concerns the fact that in the left arm there is both a soft radial artery and a sclerotic ulnar artery. If, for a moment, we assume that a soft vessel requires much less pressure for the obliteration of its lumen than a sclerotic vessel, there is the possibility that in this case a cuff over the forearm might obliterate the soft radial artery at a pressure of, let us assume, 100 mm., while 120 mm. might be needed to obliterate the lumen of the sclerotic ulnar artery. In other words, at a pressure of 100 mm. there would be no flow of blood through the radial artery, but there would be a flow and pulse through the ulnar artery. The latter pulse might then be transmitted through the superficial and deep volar arches of the palm back to the radial artery distal to the cuff, thereby giving the examiner the impression that there was still a radial pulse, so that the retrograde pulse in the radial artery would be obliterated only when the ulnar pulse was also obliterated at a higher pressure.

In the present study we eliminated this possible error by simultaneously obstructing the flow through both ulnar arteries and then determining the radial pressures. The method used for compressing the ulnar arteries was as follows: Two pieces of steel were secured, each 21 by 5 by 0.4 cm. in size. These were wrapped in cotton batting and covered with adhesive plaster. With the forearms of the patient resting on a table about 15 cm. apart and with the volar surfaces upward, each end of one piece of steel was placed across the medial half of the volar surfaces of both wrists. The other piece of steel was placed under the medial half of the dorsa of both wrists, directly underneath the upper piece of steel. A blood pressure cuff was then wrapped around both pieces of steel which were between both hands. In this way a pressure up to 300 mm. of mercury could be exerted over both ulnar arteries. Then a blood pressure cuff was placed on each forearm above the steel and the radial pressures simultaneously determined as before. With the steel compressing the ulnar arteries at a pressure around 300 mm., it was inevitable that some of this pressure should be transmitted to the adjacent radial arteries, thus lowering the values obtained over the latter. This factor would, however, be the same on both sides. As table 4 indicates, the readings of the radial arteries on both sides were almost the same, although slightly lower than the readings without ulnar compression. The foregoing experiment, therefore, is additional evidence that the sclerotic vessel is not a significant factor in the determination of blood pressure with a sphygmomanometer.

Another aspect of our results is not so easily explained. A comparison of the readings in tables 2 and 3 indicates that apparently the systolic blood pressure in our patient's brachial arteries was almost invariably a little lower than in the radial arteries, the average of all readings showing the brachial pressure 10 mm. lower than the radial pressure. This is contrary to known physiologic studies on the normal animal and the human subject; viz., normally, the blood pressure is lower in the radial than in the brachial arteries. We studied the radial and brachial blood pressures of six normal subjects with normal blood pressure and soft radial arteries by palpation and five hypertensive patients with soft radial arteries by palpation, and we found that in all but one of them the radial blood pressure was invariably lower than, or the same as, that in the brachial artery (table 5). This indicates that our technic of determination of the blood pressure in the forearms

TABLE 4.—*Simultaneous Readings of Blood Pressure of Radial Arteries After Obstruction of Blood Flow Through Both Ulnar Arteries*

June 29, 1932						June 30, 1932			
Right Radial	Left Radial	Right Radial	Left Radial	Right Radial	Left Radial	Right Radial	Left Radial	Right Radial	Left Radial
118	120	120	130	120	122	107*	102†	84	84
118	120	122	134	128	124	104*	102†	100*	90
124	124	124	118	122	130	106*	106†	112*	94
94	130	118	112	138*	138†	106*	102†	112*	96
140	126								

* Right ulnar artery not compressed.
† Left ulnar artery not compressed.

was satisfactory. In one of these subjects (case 11, table 5) who was the exception, a man of 64, with a blood pressure of 150 systolic and 88 diastolic, with soft radial arteries, the radial blood pressure was from 4 to 8 mm. higher than the brachial. We then studied similarly three subjects, aged 64, 72 and 73, respectively, in two of whom the radial and brachial arteries were markedly thickened and beaded, and in one of whom there was only a moderate degree of sclerosis. In all three cases the radial readings were higher than the brachial readings (table 5), and the greatest difference (80 mm.) was found in case 14, the subject with the most marked arteriosclerosis of the radial arteries.

It is difficult to explain these contradictory findings. Postmortem studies have shown that arteriosclerotic changes are more marked in the distal parts of the extremities, and in our patient this was true both clinically and by roentgen examination. However, our studies in this patient have shown that arteriosclerosis has no effect on the blood pressure readings. Therefore, a slightly higher blood pressure in our patient's radial than in his brachial arteries could not be due to this greater degree of arteriosclerosis in the periphery. Arteriosclerosis

TABLE 5.—*Blood Pressure Readings Simultaneously Made Over Both Brachial Arteries, Followed by Readings of Radial Arteries, then Brachial, Etc.; Eleven Subjects with Soft Radial Arteries and Three Subjects with Sclerotic Radial Arteries*

	Subjects with Soft Radials*											Subjects with Calcified Radials					
	Case 1		Case 2		Case 3		Case 4		Case 5		Case 6	Case 7	Case 8	Case 9	Case 10		Case 11		Case 12		Case 13		Case 14	
Age..... ..	24		26		26		27		28		51	54	55	50	60		64		55		72		72	
	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R. L.	R.	R.	R.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.
Brachials.....	106	106	130	122	106	96	116	112	110	108	108 116	215;118	150;90	184;96	228	226	154	150	136;70	130;76	134	138	212	186
	108	108	126	124	104	100	118	112	112	110	108 114		150;90		228	228	154	154	134;76	134;80	136	132	210	182
	110	110	128	126	102	94	118	118	116	112	104 120				230	226	148	148	130;74	132;78	136	134	188	188
	108	108	126	126			114	110	116	112	98 118				230	230							188	178
			126	124							102 118												184	178
											106 118												188	174
											106 118												186	176
																							184	176
Radials.....	96	90	112†	122	96	100	112	104	112	98	120 108	200;110	148;90	186;100	216	218	160	154	130;50	140;98	150	142	290	210
	98	90	114	126	96	100	106	104	108	104	118 120		148;90		212	218	166	152	138;86	140;88	148	138	300	210
			118	118			108	102	112	104	110 120						154	164	130;86	140;96	148	144	282	210
			118	116			110	106	104	106	106 114						150	150			144	140	300	220
			126	128																				
Brachials.....	106	108	132	122	104	104	120	114	110	108	108 118	210;114	.....	.....	228	222	148	146	124;70	130;78	128	128	184	172
	108	108	128	120			116	112	120	110					218	214	146	146			128	130		
			130	122			112	112	104	104														
									118	116														
Radials.....	98	88	126	128	...	...	106	104	106	104	112 106	204;116	.....	.....	200	214	156	150	134*†	142	138	138	260	208
	94	90					112	102	106	102	110 104				200	216	150	156			142	142		
	90*†	86†					110	114	106	102	110 110													
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							104	110																
Brachials.....	108	104	124	132	...	....	...	...	114	110	116 114	218;118	.....	.....	226	224	146	146	.....	.....	128	138		
	108	104	122	124											226	224	146	146			124	132		
	110	102	132	132																	128	130		
	106	100																						
Radials.....	96	94	...	...	...	....	...	...	...	...	... ...	198;118	.....	.....	...	...	...	..	.....	.....	140	142		
	90	86																						

* All by auscultation.
† By palpation.

does not explain why the blood pressure in the soft radial was higher than that in the corresponding sclerotic brachial artery. The fact that most of the time we used the palpatory method for the radial and the auscultatory method for the brachial arteries is to be noted, but this might tend to give an even lower reading for the radial and, therefore, does not explain our results. On the first day we used auscultation for both radial and brachial arteries and still found the radial readings higher. In the patients with marked sclerosis, the auscultatory method revealed practically no sounds at any level of pressure over the radial arteries. Our suggestion for being able to feel an impulse in the radial arteries of patients 12, 13 and 14 when the pressure in the cuff over these arteries was as much as 100 mm. higher than the known blood pressure (table 5) is that we were feeling a transmitted shock which passes from the pulse above the cuff over the rigid empty vessel under the cuff and on to the examiner's finger. The more marked the sclerosis, the easier is the transmission. This possibility is further borne out by the fact that in case 14, although we could feel an impulse over the right radial artery at 300 mm., the Tycos recording apparatus did not record a pulse wave above 200 mm. This could mean only that at 300 mm. we were not dealing with an expansile pulsation, but rather with a transmitted vibratory impulse which could not be recorded on the Tycos oscillometer.

SUMMARY AND CONCLUSIONS

Simultaneous bilateral readings of the blood pressure in the radial arteries were made in a patient who both clinically and radiographically had a soft radial vessel on one side and a sclerotic radial vessel on the other side. Our results are in accord with evidence obtained previously in studies with excised vessels, and our observations indicate that the sclerotic arterial wall has no significant effect on the determination of blood pressure. It was also found that in this patient, as well as in three other patients with marked radial sclerosis, the radial blood pressure reading was higher than the brachial blood pressure reading.

371 Commonwealth Avenue.

CLINICAL STUDIES OF RESPIRATION

I. PLETHYSMOGRAPHIC STUDY OF QUIET BREATHING AND OF THE INFLUENCES OF SOME ORDINARY ACTIVITIES ON THE EXPIRATORY POSITION OF THE CHEST IN MAN

J. A. GREENE, M.D.
IOWA CITY
AND
H. C. COGGESHALL, M.D.
INDIANAPOLIS

Alterations in the respiratory movements may consist in a change in the rate, rhythm or amplitude of the respirations or in the expiratory position of the chest, or in several of these combined. The factors that influence the rate, rhythm and amplitude of the respirations have been carefully studied by numerous investigators, and the subject has been thoroughly reviewed by Haldane,[1] Gesell [2] and Means,[3] but the factors that alter the expiratory position of the chest have received less study.

Changes in the expiratory position of the chest were encountered during a study of oxygen debt after muscular work in patients with hyperthyroidism. The consumption of oxygen as determined by the closed circuit method increased rapidly during work, whereas immediately after work it decreased to or below the previous basal level, so that a lack of oxygen was not demonstrable. The respiratory quotient declined during work to 0.7 or below, and increased after work to 1 or above. These observations could not be explained entirely by the change in the caloric value of oxygen or by a decreased excretion of carbon dioxide during work, but could be explained by a storage of oxygen in the body during work, with some utilization of this stored oxygen after work. Since Bohr [4] and Rubow [5] showed that the vital

From the Lilly Laboratories for Clinical Research, Indianapolis City Hospital, and the Department of Medicine, Indiana University.

1. Haldane, J. S.: Respiration, New Haven, Conn., Yale University Press, 1927.

2. Gesell, R.: The Chemical Regulation of Respiration, Physiol. Rev. **5**:551, 1925.

3. Means, J. H.: Dyspnoea, Medicine **3**:309, 1924.

4. Bohr, C.: The Functional Variations in the Middle Position and Vital Capacity of the Lung: Normal and Pathological Emphysema, Deutsches Arch. f. klin. Med. **88**:385, 1906-1907.

5. Rubow, V.: Study of the Respiration of Heart Disease: A Contribution to the Study of the Pathology of the Lesser Circulation, Deutsches Arch. f. klin. Med. **92**:255, 1907.

middle position of the chest (*Mittellage*) increased after work, a sphygmomanometer cuff attached to a tambour was fastened around the chest to determine the relative volumes of the chest before, during and after work. This study showed an increase in the volume of the chest during work and a decrease after work.

Since changes in the volume of air in the lungs at the end of expiration may alter the effective ventilation of the lungs, it is desirable to study the factors that cause this alteration in the respiratory movements.

Davy [6] was the first to determine the residual air of the lungs in the living, and Hutchinson,[7] by the use of the spirometer, was the first to study the vital capacity. Bohr,[4] Rubow,[5] Siebeck [8] and Bittorf and Forschback [9] emphasized the vital middle position of the chest, while Peabody and Wentworth [10] showed the relation of the vital capacity to dyspnea. Lundsgaard and Van Slyke [11] improved the technic for the determination of the residual air of the lung and studied the different components of the external respiration, but these methods do not give a continuous record of the relative volumes of the chest, and therefore sudden changes in the volume of the chest cannot be determined.

The use of a body plethysmograph was suggested by Bohr [4] but was abandoned without a trial because he thought the gas in the gastroenteric tract might interfere. Binger and Davis [12] used a body plethysmograph to study the respirations of patients with pneumonia, but the entire body, with the exception of the head and neck, was enclosed in the apparatus, and it was therefore not suitable for this study.

METHOD

A body plethysmograph was constructed by means of a rubber bag covered with sateen. The bag was made from large, thin sheets of pure gum rubber and designed to cover the anterior and lateral surfaces of the body from the neck to the pubis and to project onto the shoulders. Its shape is shown in figure 1.

6. Davy, H.: Collected Works of Sir Humphry Davy, London, Smith, Elden & Co., 1839, vol. 3, p. 236.

7. Hutchinson, J.: Tr. Med.-Chir. Soc. Edinburgh **29**:137, 1846.

8. Siebeck, R.: On the Influence of the Respiratory Mechanism Through Diseased Conditions of Respiration and Circulation, Deutsches Arch. f. klin. Med. **100**:205, 1910.

9. Bittorf, A., and Forschback, J.: Investigation upon the Lungs Filling up in Sickness, Ztschr. f. klin. Med. **70**:474, 1910.

10. Peabody, F. W., and Wentworth, J. A.: The Vital Capacity of the Lungs and its Relation to Dyspnea, Arch. Int. Med. **20**:443 (Sept.) 1917.

11. Lundsgaard, C. C., and Van Slyke, D. D.: Studies of Lung Volume: Relation Between Thorax Size and Lung Volume in Normal Adults, J. Exper. Med. **27**:65, 1918.

12. Binger, C. A. L., and Davis, J. S., Jr.: Body Plethysmograph for Study of Respiratory Movements in Human Beings, Proc. Soc. Exper. Biol. & Med. **25**:607, 1928.

The projections onto the shoulders were fastened by straps, which were crossed in the back; these, like the strap around the pelvis, were fastened snugly about the body. The remaining straps were tightened just enough so that when the subject was in the supine position, the lateral margins of the rubber bag were brought into line with the junction of the subject's back and the bed. The bag was connected to a spirometer by a large hose, and the movements of the spirometer were recorded on kymograph paper ruled in millimeters. After the

Fig. 1.—The shape of the body plethysmograph when deflated.

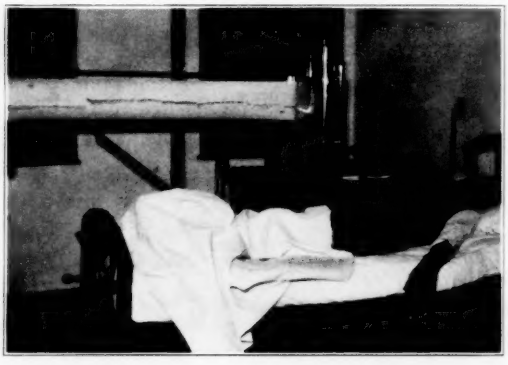

Fig. 2.—The plethysmograph applied to a subject.

bag was fastened to the body and connected to the spirometer, it was tightly filled with air to eradicate any wrinkles, and the pressure in the apparatus was adjusted by the addition of a weight of 300 Gm. to the top of the spirometer bell. The apparatus is shown applied to a subject in figure 2.

The design of the plethysmograph was later changed in an attempt to make the outer wall more rigid. A wooden cradle was constructed, which extended from the axillae to the pubis, at from 8 to 10 inches (20 to 25 cm.) above the body. The cradle was lined with sateen, which projected forward and was fastened

around the neck of the subject. The caudad end was fastened snugly around the pelvis. The hose connected to the rubber bag was fastened to the top of the cradle.

The accuracy of the apparatus was determined on forty subjects by simultaneous records with a spirometer attached to the mouth. Both spirometers had a volumetric equivalent of 20.73 cc. per millimeter change in the height of the spirometer bell. The movement of the bell of the plethysmographic spirometer varied with different subjects and with different applications of the apparatus to the same subject. When the change in volume was large, it compared favorably with the spirometer attached to the mouth; the movement of 1 mm. on the plethysmographic record was equivalent to an average change of 23.5 cc. of air in the lungs, the range being from 22 to 26 cc. With the smaller changes in volume which were encountered in quiet breathing, the volumetric range was from 22 to 42 cc. with different persons and with different applications of the apparatus to the same person. However, when the volumetric value of a change of 1 mm. on the plethysmographic record was determined two or more times during the same application of the plethysmographic bag, it never varied over 5 cc., or 16.6 per cent. A few subjects were encountered who persistently showed only small changes in the movement of the plethysmographic record. The reason for this is not known; most of these subjects, however, were obese and had shallow respirations.

False results, particularly as related to the expiratory position of the chest, may be obtained by any external pressure on the rubber bag, e.g., through adduction of the arm or flexion of the neck.

Although the volumetric values obtained by this method vary with the depth of respiration, with different persons and with different applications of the bag in the same person it still permits the continuous study of the relative volumes of the lungs with a certain degree of accuracy when standardized with each application of the apparatus.

RESULTS AND COMMENT

Expiratory Position of the Chest During Quiet Breathing.—During breathing in repose, in a majority of the subjects the expiratory position of the chest was more constant than the inspiratory position. This is in accord with the findings of Hendry, Carpenter and Emmes.[13] Figure 3, graph A, shows the most common type of quiet breathing. The down stroke is expiration, and the graph is read from right to left. The expiratory position is shown to be almost constant. Graph B shows a fluctuating expiratory position of the chest, which was encountered in a few apparently normal persons and which has been called undulatory breathing.

It was shown by Musso[14] that the respirations of normal adults in repose were fairly regular in rhythm, amplitude and "muscular tone," but that the depth of inspirations may vary in a rhythmical way and that this is more common in young and elderly persons. Conner and

13. Hendry, M. F.; Carpenter, T. M., and Emmes, L. E.: Gaseous Exchange with Unpractised Subjects and Two Respiratory Apparatus Employing Three Breathing Appliances, Boston M. & S. J. **181**:285 (Sept. 4), 334 (Sept. 11) and 368 (Sept. 18) 1919.

14. Musso: La respiration periodique et la respiration superflue ou de luxe, Arch. ital. de biol. **7**:48, 1866; quoted by Conner and Stillman.[15]

Stillman [15] observed undulatory breathing in some normal persons and a more marked disturbance of the same type in patients with meningitis. Changes in the expiratory position of the chest during undulatory breathing have also been shown by Neilson and Roth.[16] Periodic breathing and periodic irregularities in the respirations of some subjects in repose were observed by Reed and Kleitman,[17] but the irregularity usually disappeared during sound sleep. Conner and Stillman [15] stated that in elderly persons undulatory breathing is more pronounced during sleep. The subjects of our study were from 20 to 50 years of age, and only a few were studied during sleep. In those studied, the character of the respiration and the changes in the volume of the thorax

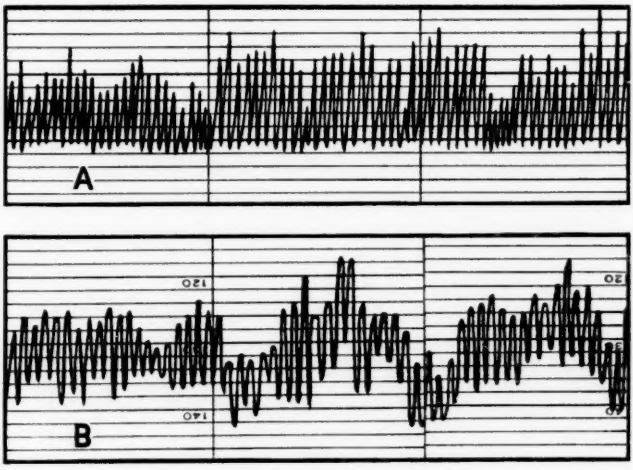

Fig. 3.—*A*, the most common type of quiet breathing; *B*, fluctuating expiratory position of the chest.

were of the same type during sleep as in the basal state, but the actual changes in volume were decreased. One subject who had fluctuations of the expiratory position in the basal state exhibited the same fluctuations during sleep, but to a lesser degree, as shown in figure 4 (graph A). The graphs are read from right to left, and the down stroke indicates expiration. This patient snored at irregular intervals; the effect of the

15. Conner, L. A., and Stillman, R. G.: A Pneumographic Study of Respiratory Irregularities in Meningitis, Tr. A. Am. Physicians **26**:464, 1911.

16. Neilson, J. M., and Roth, P.: Clinical Spirography, Arch. Int. Med. **43**:132 (Jan.) 1929.

17. Reed, C. I., and Kleitman, N.: Studies on Physiology of Sleep: IV. Effect of Sleep on Respiration, Am. J. Physiol. **75**:600, 1925.

snoring on the respirations is shown in graph B at 1 and 2. At the end of the apnea, at 2, the subject jumped as though startled, and then hyperpnea began. After the subject was awakened, he stated, without being questioned, that he had dreamed that some one was choking him and that he "had to get free to breathe."

Effect of Changing the Body Position on the Expiratory Position of the Chest.—The influence of changing the body from the horizontal to the vertical position was studied first by Panum [18] and later by Loven.[19] The results varied, and the interpretation was a disputed point between these investigators. The differences in the results may have been due to the methods employed and to the length of time

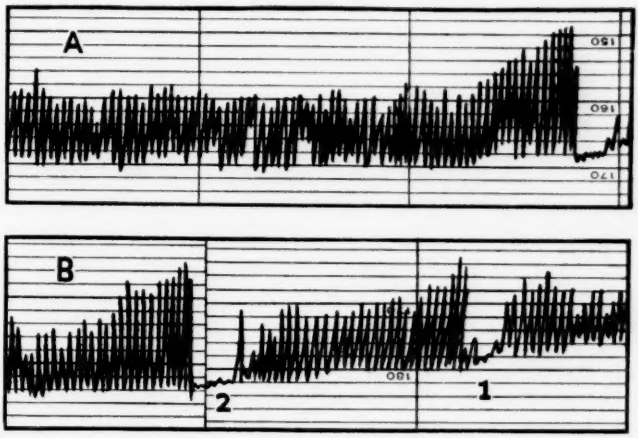

Fig. 4.—*A*, fluctuation of the expiratory position during sleep; *B*, at 1 and 2, effect of snoring on respirations.

necessary for the effect to become manifest after the change in body position. Bohr [4] found that the vital middle position was increased when the body was changed from the horizontal to the vertical position. He obtained this increase when the body was changed from the horizontal to the sitting position, but there was no further increase when changed from the sitting to the standing position. The time necessary for the appearance of this increase varied, requiring several minutes in some instances.

Since the plethysmographic method gives a continuous record of the changes in the relative volume of the chest, the influence of changing the body position was studied to learn if this method would record

18. Panum, P. L.: Arch. f. d. ges. Physiol. **1**:125, 1868; quoted by Bohr.[4]
19. Loven, C.: Nord. med. ark. **4**:1, 1872; quoted by Bohr.[4]

the changes in volume due to changes of the body position, the length of time necessary for the effect to be obtained and, lastly, the accuracy of the plethysmographic method when used to measure this effect.

A record of the quiet breathing was obtained with the subject in the supine position on a tilting table. The body position was altered by tilting the table to the vertical or horizontal positions.

Bohr [4] and others had shown that muscular exertion increases the middle position, but in our study the only muscular exertion performed was that necessary for the support of the body weight in the vertical position.

The increase of the expiratory position of the chest due to the change of the body from the horizontal to the vertical position and the decrease of the expiratory position of the chest when the body was returned to the horizontal postion are shown in figure 5, graphs A and B. The graphs are read from right to left; the down stroke indicates expiration. Graph A is a plethysmographic record taken simultaneously with the spirographic record, graph B. At 1, the change to the vertical position was begun; at 2, the vertical position was assumed; at 3, the change to the horizontal position was begun, and at 4, the horizontal position was assumed.

The changes in the volume of the thorax when the body position was changed were almost instantaneous when the subject was relaxed. In all three of the subjects studied, however, the volume changes that occurred with the change of body position varied until the subject had become accustomed to the procedure. In some instances, the volume decreased when the body was changed to the vertical position, and there was an increase in volume when it was returned to the horizontal position; in some instances there was no apparent change in the volume even after eight minutes. The change in volume apparently depends on the balance in tone of the muscles of the thorax, abdomen and diaphragm. Undoubtedly, there was not complete relaxation when these varied results were obtained, because the subjects were not accustomed to the sensations derived from the procedure. When the body was changed from the horizontal to the vertical position, there was in the abdomen a sensation of "sinking" similar to that obtained when one goes up in a rapidly moving elevator, and when the body was changed back to the horizontal position there was a "rising" sensation in the abdomen such as is encountered when one goes down in a rapidly moving elevator. A compensatory change in the tone of the muscles undoubtedly occurred, as illustrated by figure 5, graph C. Graph C is a plethysmographic record of the respirations before the subject became accustomed to the procedure. Inflation occurred when the body was changed from the horizontal to the vertical position. This procedure was begun at 1, and was completed at 2. Deflation occurred almost

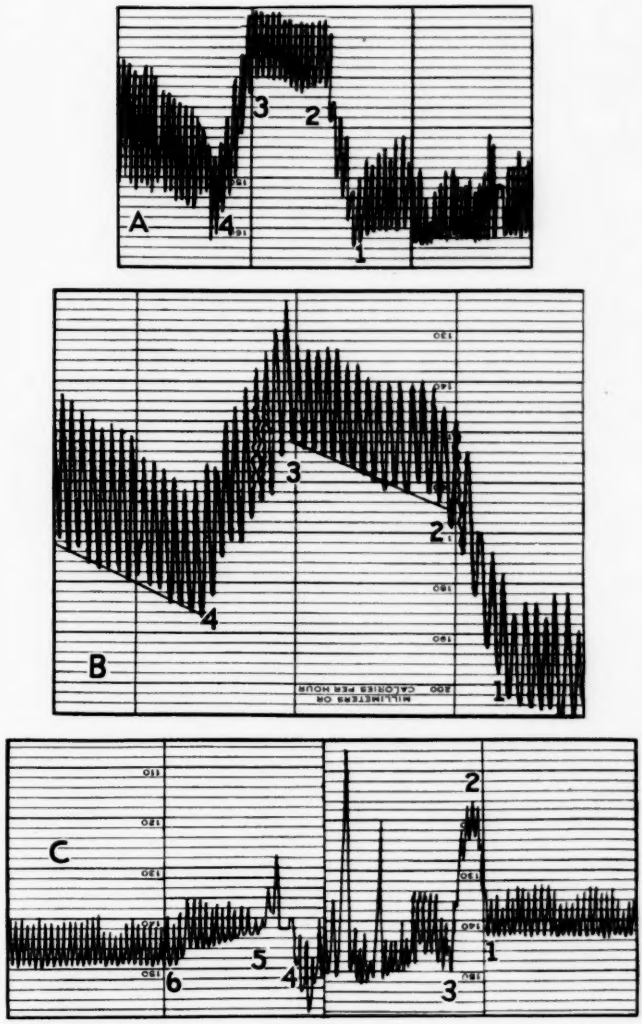

Fig. 5.—Effect of change of body position on the expiratory position of the chest: *A*, plethysmographic record; *B*, spirographic record; *C*, period of adiustment to changed position.

immediately, without further change in the position of the body, and was completed at 3. The respirations were altered in character during the time the body was in the vertical position. A slight inflation occurred when the body was returned to the horizontal position, which was begun at 4 and completed at 5. About one minute was required before the respirations became normal at 6.

This variation in tone of the diaphragm, thoracic and abdominal muscles would explain Bohr's observations of the variations in the length of time necessary for characteristic changes to occur, and also why Panum and Loven obtained varying results, since their studies were made at short intervals.

The accuracy of the plethysmographic method for determining the expiratory position of the chest due to changes in the position of the body was determined by the simultaneous spirographic and plethysmographic records, shown in figure 5, graphs A and B. The volume of the air in the chest increased 891.4 cc. by the spirographic method and 870.6 cc. by the plethysmographic method when the body was changed from the horizontal to the vertical position.

Effect of Slight Muscular Work on the Expiratory Position of the Chest.—Bohr [4] and others showed that slight muscular work will increase the middle position of the chest, but the methods employed did not give continuous records of the relative volumes of the chest; therefore it was not known when this increase occurred. Bohr [4] considered this increase to be a compensatory mechanism that widened the capillaries of the lung and aided the circulation, whereas Bittorf and Forschback [9] thought it to be a reflex phenomenon which, in some instances, was detrimental to the proper gaseous exchange.

To study the influence of muscular exertion on the expiratory position of the chest, a record of quiet breathing was obtained with the subject in the supine position. The subjects were cautioned against dorsal flexion of the spine and against forward projection of the chest wall. A measured amount of muscular work by flexion of the forearm against an ergograph was then performed.

The influence of muscular work on the expiratory position of the chest is shown in figure 6. An increase in the expiratory position is shown in graphs A, B and C, while graphs D and E show no effect during muscular work. Graph A, B and D are plethysmographic records. Graph C and E are spirographic records. Graphs B and C and graphs D and E are simultaneous records. Work was begun at 1 and was discontinued at 2.

In the two subjects who showed an increase in volume of the chest, the volume increased immediately after work was begun. With the second subject (graphs B and C), the volume decreased slightly after the initial increase and returned to its previous level immediately after

work ceased, while with the first subject (graph A) the volume continued to increase as long as work was performed and had not returned to its previous level five minutes after the work had ceased.

These observations indicate that the increase of the volume of air in the chest at the end of expiration during work may be a reflex mechanism; however, when the arm is flexed at the elbow, some of the

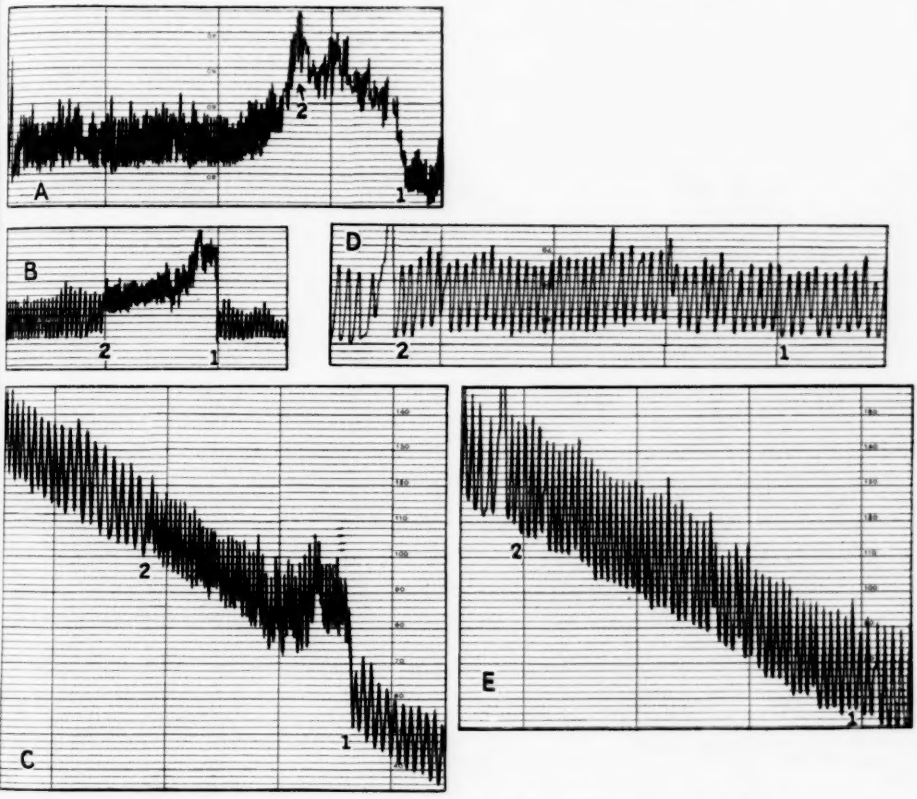

Fig. 6.—Influence of muscular work on the expiratory position of the chest.

muscles of the shoulder girdle contract, and this may have exerted an influence to change the volume of the thorax. In order to decrease or exclude this factor, the subject gripped the hand against a dynamometer, and the influence on the expiratory position was determined. There was an increase in the volume of the thorax when the hand was gripped, as shown in figure 7. This increase is not simply an inspiration, because the respiratory motions are continued during the inflation.

Graphs A and B are plethysmographic records of the respirations. The expiratory position of the chest increased when the hand was gripped at 1, and decreased after the hand was relaxed at 2.

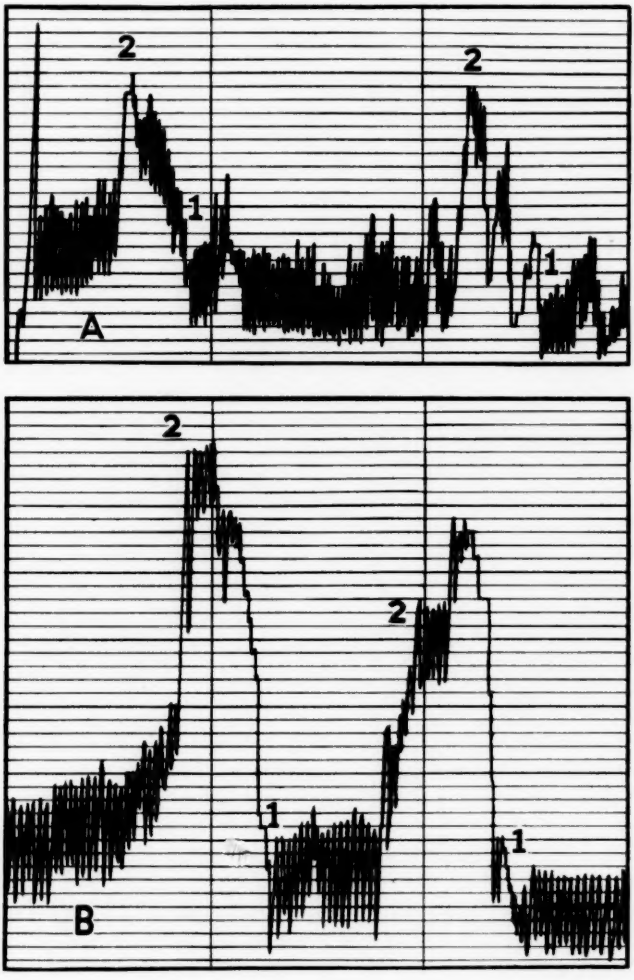

Fig. 7.—Influence exerted on the expiratory position when the subject gripped a hand against a dynamometer.

Care must be taken, however, to prevent adduction of the arm against the plethysmographic bag, or false results will be obtained.

Influence of Short Periods of Talking and Reading on the Expiratory Position of the Chest.—Because the use of the voice apparently alters the respirations more than any of the ordinary activities, the influence of talking and reading aloud was studied, and the results are shown in figure 8. The graphs are plethysmographic records; talking began at 1 and ceased at 2. In graph B, reading aloud began at 3 and ceased at 4. The speed of the kymograph was one half as great in graph B as in graph A.

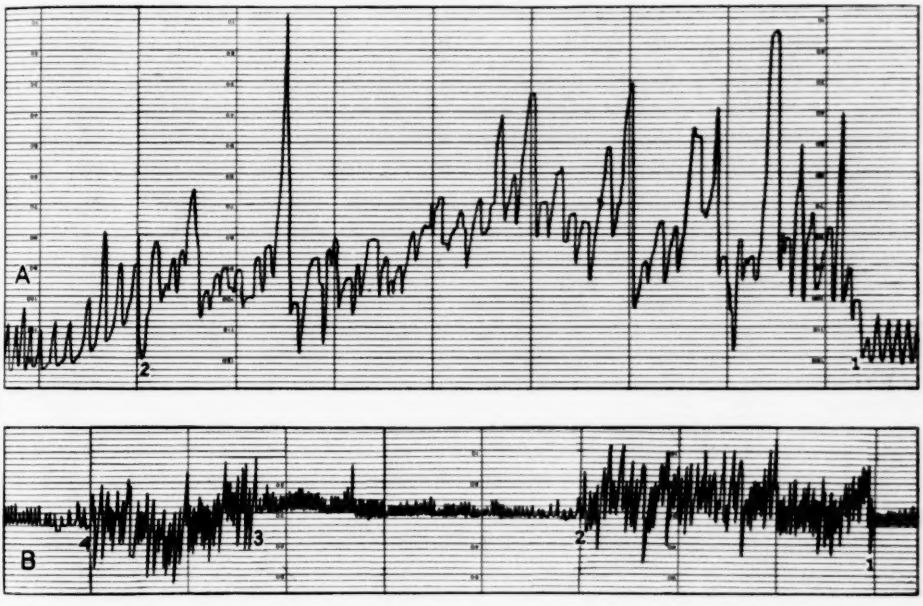

Fig. 8.—Influence of talking or reading aloud on the expiratory position.

The speech of the first subject was faltering, the sentences were short, the trend of thought was not connected, the subject appeared bashful, and the expiratory position increased markedly. The second subject was at ease, the sentences were long, the thought was connected, and the expiratory position varied. The end of expiration appeared to be controlled by the pauses in the sentence and at the end of the sentence. In graph B, following talking and reading, there was a definite decrease in the frequency and amplitude of the respirations, which indicated that an excess amount of carbon dioxide was eliminated during the periods of talking.

SUMMARY

1. A plethysmographic method for the study of the respiratory movements in man has been described.

2. The expiratory position of the chest in repose is more constant than the inspiratory position, but the expiratory position may also fluctuate in apparently normal subjects.

3. After the subject has become accustomed to the procedure, the volume of air in the lungs at the end of expiration increases immediately when the body is changed from the horizontal to the vertical position and decreases immediately when the body is returned to the horizontal position.

4. The expiratory position of the chest may or may not increase with slight muscular work. If it increases, the time required for it to return to its previous level varies.

5. The false results obtained by the method are discussed.

6. The expiratory position of the chest and the depth of the respirations during talking and reading aloud appear to depend on the length of the sentences and phrases when the subject is at ease and when hyperventilation may occur.

THE QUESTION OF THE PRESENCE OF A PRESSOR SUBSTANCE IN THE BLOOD IN ESSENTIAL HYPERTENSION

G. E. WAKERLIN, M.D., PH.D.
AND
H. D. BRUNER, S.B.
LOUISVILLE, KY.

The etiology of essential hypertension is still obscure. Perhaps subsequent research will disclose multiple etiologies and will demonstrate the term to be generic rather than specific. Among the numerous postulates that have been advanced to explain the genesis and maintenance of the hypertension which is pathognomonic of this disease is that of the possible presence of a pressor substance in the blood. Thus Danzer, Brody and Miles [1] found a rise in blood pressure after the intravenous injection of unchanged specimens of blood from patients with hypertension into atropinized cats that had been desensitized to human blood, and concluded that there is a pressor substance in the blood in hypertension. Using the same technic, Danzer [2] later reported similar results from a majority, but not from all, of the tested specimens of blood of patients with hypertension. On the other hand, Stewart [3] obtained no pressor effects from the intravenous injection of serums from patients with hypertension into dogs, and Bröking and Trendelenburg [4] found no increase in the vasoconstricting properties of hypertensive blood serums, as compared with normal serums, by means of perfusion experiments on frogs. Curtis, Moncrieff and Wright,[5] moreover, found no definite pressor effects from the intravenous injection of specimens of hypertensive blood into atropinized cats that were desensitized to human blood. Likewise, Hülse [6] was unable to obtain a rise in the blood pressures of

From the Department of Physiology and Pharmacology, University of Louisville School of Medicine.

1. Danzer, C. S.; Brody, J. G., and Miles, A. L.: Proc. Soc. Exper. Biol. & Med. **23**:454, 1926.
2. Danzer, C. S.: Am. J. Physiol. **81**:472, 1927.
3. Stewart, G. N.: J. Exper. Med. **14**:377, 1911.
4. Bröking, E., and Trendelenburg, P.: Deutsches Arch. f. klin. Med. **103**: 168, 1911.
5. Curtis, F R.; Moncrieff, A. A., and Wright, S.: J. Path. & Bact. **30**:55, 1927.
6. Hülse, W.: Arch. f. exper. Path. u. Pharmakol. **146**:282, 1929.

dogs by injecting specimens of hypertensive blood into the carotid or vertebral arteries. Furthermore, he found that the intrathecal injection of serums from patients with essential hypertension produced no increase in the blood pressures of cats.

In view of the conflicting nature of the evidence thus far adduced, we decided to study the problem by employing the more direct technic of observing the action of hypertensive and normal blood serums on the tone of arterial rings. This procedure offered an advantage over methods which employ the whole animal in that the latter, because of regulatory vasomotor mechanisms operating in the intact organism, may fail to demonstrate the pressor substance, even if it is present. However, our method offers the possibility of detecting only a circulating substance affecting the peripheral vascular tree and not one possessing central action.

As is well known, coincident with the clotting of blood, epinephrine-like substances arise in the serum.[7] We therefore looked for possible significant quantitative differences between the tone-augmenting properties of hypertensive serums and normal serums for arterial rings.

PROCEDURE

The apparatus employed was essentially that used by Meyer [8] in his study of the physiology and pharmacology of arterial segments and by Cow,[9] Barbour [10] and Voegtlin and Macht [11] in their investigations of the action of drugs on arterial segments. Rings about 4 mm. in diameter and 3 mm. in width, obtained from the tertiary division of the superior mesenteric artery of freshly slaughtered beeves, were placed in a glass chamber filled with Locke's solution at 37.5 C. The superior mesenteric branch was selected because it is known to contain relatively more smooth muscle and less elastic tissue than the carotid or the vertebral arteries, and hence was believed to be structurally more analogous to the arterioles. Oxygen was bubbled through the fluid medium bathing the arterial segment. One side of the ring was attached to the bottom of the chamber, and the other was connected to the short arm of a lever delicately balanced on a knife-like edge. The lever magnified changes in the tone of the arterial rings twenty-three times. The bottom of the chamber was drawn out and connected with rubber tubing so that the fluid in the chamber could be changed at will. The chamber was immersed in a water-jacket which maintained the temperature at a constant level.

When first set up, the arterial segment was in a state of considerable tonus, which was partially overcome by a load of 2 Gm. attached to the long arm of the lever at the same distance from the fulcrum as the attachment of the artery on the short arm. The process of relaxing the arterial ring usually took about one hour. At the end of this period, the diameter of the segment was from 6 to 8 mm. After

7. O'Connor, J. M.: Arch. f. exper. Path. u. Pharmakol. **67**:195, 1912.
8. Meyer, O. B.: Ztschr. f. Biol. **43**:352, 1906.
9. Cow, D.: J. Physiol. **42**:125, 1911.
10. Barbour, H. G.: J. Exper Med. **15**:404, 1912.
11. Voegtlin, C., and Macht, D. I.: J. Pharmacol. & Exper. Therap. **5**:77, 1913.

the elasticity of the artery had reached an equilibrium, the preparation was ready for testing, the 2 Gm. weight being used as a lifting, as well as a stretching, load.

Blood serums from thirty patients with essential hypertension and from fifteen with normal blood pressures were studied. The patients were equally divided between the two sexes. In twenty of those with hypertension, symptoms were manifested that occur relatively late in the course of the disease. Each member of this group had experienced one attack of cardiac decompensation and was receiving maintenance doses of digitalis at the time when the specimen of blood was drawn. In the remaining ten patients with hypertension the condition was in a comparatively early stage. Five of these patients were free from symptoms so far as hypertension was concerned. The other five showed a mild degree of cardiac insufficiency which came under class 1 of the nomenclature for functional capacity approved by the American Heart Association.[12] The blood pressures of the entire hypertensive group ranged from 160 systolic and 94 diastolic to 300 systolic and 150 diastolic, with an average of 194 systolic and 115 diastolic. The results of urinalyses and of studies of the blood chemistry in all of the cases of hypertension were uniformly normal. The results of phenolsulphonphthalein tests on the group with late hypertension and of urine concentration tests (Mosenthal) on ten of the patients in this group were normal. No other studies of renal function were made. Retinal and peripheral arteriosclerotic changes were absent or were slight. The fifteen patients with normal blood pressures were the subjects of a miscellany of diseases unrelated to the cardiovascular system. In general, these patients belonged to the same age group as the hypertensive patients.

Fifteen separate experiments were made, arterial segments from a corresponding number of beeves being used. One normal and two hypertensive serums were employed for each experiment. After a kymographic record of the tone of the arterial ring in Locke's solution had been obtained, Locke's solution was replaced by one of the serums. The tone of the ring promptly increased. After an interval of twenty minutes, the serum was removed and Locke's solution was again added. The change back to Locke's solution resulted in a return of the arterial ring to its original tonus. Subsequently, the same procedure was used for the other two serums. In the different experiments the order of adding the hypertensive and normal serums was varied. At the conclusion of each experiment, the first serum tested was again added to the bath in order to demonstrate that there had been no appreciable change in the motor activity of the arterial ring or in the tone-augmenting properties of the serum for the arterial segment. This alternate contraction and relaxation of the arterial ring on the addition of serum and then of Locke's solution is similar to that described by Friedberger[13] for his mammalian perfusion experiments with serums and Ringer's solution

RESULTS

When the arterial rings were partially relaxed, one third of them showed in Locke's solution the spontaneous tonal changes illustrated in chart 1. The rhythmic oscillations varied somewhat in rate in different experiments, but in general averaged about one every two minutes.

12. New York Tuberculosis and Health Association, Criteria for the Classification and Diagnosis of Heart Disease, New York, J. J. Little & Ives Company, 1929. p. 11.

13. Friedberger, E.: Klin. Wchnschr. **6**:1047, 1927.

When Locke's solution was replaced by serum, the arterial segment, whether previously active or not, showed a prompt and sustained increase in tone, as illustrated in chart 2. When the serum was drained off and Locke's solution was again added, the arterial segment gradually returned to its original tonus (chart 2). This occurred in from ten to forty minutes. In almost every instance, when the serum

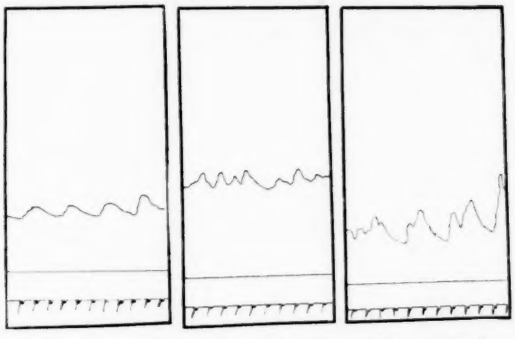

Chart 1.—Spontaneous tonus changes in three different beef arterial rings immersed in Locke's solution at 37.5 C. Intervals of one minute are recorded at the bottom.

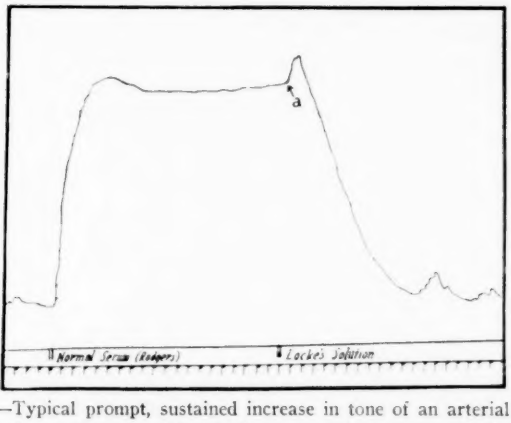

Chart 2.—Typical prompt, sustained increase in tone of an arterial segment on the addition of normal serum, followed by a somewhat more gradual relaxation of the segment on replacement of the serum by Locke's solution. The transient augmentation in tonus labeled *a* was almost invariably observed when the serum was replaced by Locke's solution. The artery shows spontaneous variations in tonus. Intervals of one minute are recorded at the bottom.

was replaced by Locke's solution, the relaxation of the arterial ring was preceded by the transient augmentation in tone labeled *a* in chart 2.

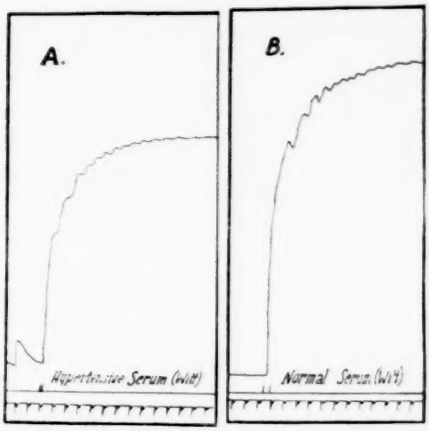

Chart 3.—Rhythmic changes in the tone of two arterial segments during the latter part of the increase in tone following the addition of serum. Segment *A* showed spontaneous motor activity. Segment *B* did not. A hypertensive serum was added to *A*. A normal serum was added to *B*.

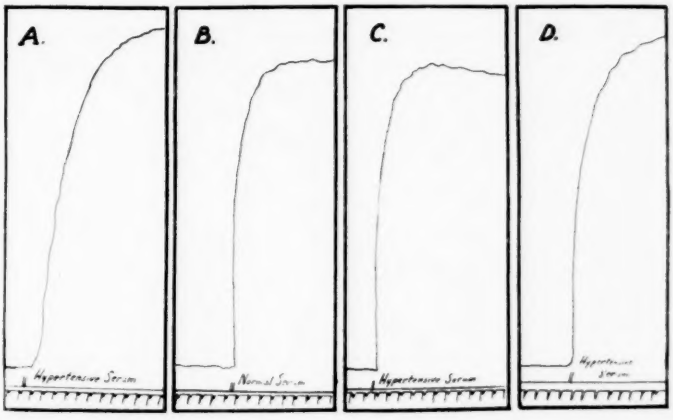

Chart 4.—Increases in the tone of an arterial segment produced successively (*A*) by a hypertensive serum from B. R. with a blood pressure of 224 systolic and 114 diastolic; (*B*) by a normal serum from G. K. with a blood pressure of 118 systolic and 80 diastolic, and (*C*) by a hypertensive serum from S. C. with a blood pressure of 282 systolic and 102 diastolic. *D* shows the increase in tone produced by a second addition of the first hypertensive serum from B. R. at the end of the experiment.

One third of the arterial rings showed a peculiar series of small rhythmic contractions and relaxations during the latter part of the increase in tonus following the addition of serum to the glass chamber. These rhythmic changes are illustrated in chart 3. They occurred at the rate of about three every two minutes and were observed in

Increases in the Tone of Beef Arterial Rings Produced by Serums from Patients with Essential Hypertension and Serums from Patients with Normal Blood Pressures

	Serums from Patients with Late Essential Hypertension		Serums from Patients with Normal Blood Pressures	
Experiment	Blood Pressure Readings, Systolic/Diastolic	Increases in the Tone of the Arterial Rings as Measured by the Rise of the Writing-Point of the Lever, Cm.	Blood Pressure Readings, Systolic/Diastolic	Increases in the Tone of the Arterial Rings as Measured by the Rise of the Writing-Point of the Lever, Cm.
1	210/120 200/110	8.3 8.2	124/82	7.1
2	160/ 94 170/ 90	9.4 11.5	124/80	10.4
3	170/120 198/120	11.9 12.0	134/84	11.5
4	300/150 200/124	7.4 5.1	115/90	6.7
5	220/130 170/100	4.1 5.0	120/70	5.5
6	205/130 188/110	7.7 8.2	100/70	11.8
7	220/150 160/100	8.7 8.1	100/60	11.6
8	200/100 175/140	6.3 9.9	120/80	8.0
9	182/128 164/ 96	12.3 10.0	115/60	11.5
10	160/120 180/100	4.8 6.3	100/60	8.4
Average	191/117	8.3	115/74	9.3
	Serums from Patients with Early Essential Hypertension			
11	170/110 200/120	7.8 9.5	120/80	6.9
12	224/114 282/102	12.4 11.1	118/80	11.2
13	170/100 200/120	14.0 12.5	120/80	13.8
14	200/110 165/120	7.5 8.6	120/80	8.2
15	200/100 190/120	5.0 3.4	124/80	4.6
Average	200/112	9.2	120/80	8.9
Grand average	194/115	8.6	117/76	9.1

arterial rings which did not show the spontaneous rhythmic activity in Locke's solution previously mentioned, as well as in those which were spontaneously active.

Chart 4 illustrates a typical experiment with two hypertensive blood serums and a normal serum. The hypertensive serum from B. R., a white woman, aged 53, with a blood pressure of 224 systolic and 114

diastolic and a condition diagnosed as hypertensive disease of the heart and myocardial insufficiency, the latter too mild to necessitate digitalis medication, caused a rise of 12.4 cm. in the writing-point of the lever attached to the arterial segment. The normal serum from G. K., a white man, 41 years of age, with a blood pressure of 118 systolic and 80 diastolic and a condition diagnosed as gastric ulcer, resulted in a rise of 11.2 cm. The hypertensive serum from S. C., a Negro man, 49 years of age, with a blood pressure of 282 systolic and 102 diastolic and a condition diagnosed as hypertensive disease of the heart and early myocardial insufficiency, caused an elevation of 11.1 cm. A second addition of the first hypertensive serum from B. R. at the end of the experiment resulted in a rise of 12 cm., thus demonstrating that there had been no appreciable change in the motor activity of the arterial segment or in the tone-augmenting properties of the serum during the course of the experiment. These differences between the constricting properties of the three serums for the arterial ring were not significant.

The results obtained in the rest of the series of fifteen experiments were similar and are summarized in the accompanying table. As seen from this table, the average rise of the writing-point was 8.3 cm. for serums from the patients with late hypertension; 9.2 cm. for the serums from patients with early hypertension; 8.6 cm. for all of the serums from patients with hypertension, and 9.1 cm. for all of the serums from patients with normal blood pressure. In other words, there was no evidence of the presence of larger amounts of vasoconstricting or pressor substances in the hypertensive serums as opposed to the normal serums. Nor was there any correlation between the increase in the arterial tone produced by the various serums and the blood pressures of the patients from whom the serums were obtained.

COMMENT

The spontaneous rhythmic tonal changes in Locke's solution previously described for five of the fifteen arterial rings suggest that arterial musculature, under certain conditions at least, manifests an inherent rhythmic motor activity quite independent of extrinsic nervous connections.

Adler,[14] Hess [15] and others observed rhythmic variations in arterial tonus in vivo, and Meyer,[16] Günther [17] and Rigoni [18] noted the appear-

14. Adler, I.: J. Pharmacol. & Exper. Therap. **8**:297, 1916.
15. Hess, W. R.: Arch. f. d. ges. Physiol. **173**:243, 1919.
16. Meyer, O. B.: München. med. Wchnschr. **57**:1571, 1910.
17. Günther, G.: Ztschr. f. Biol. **65**:401, 1915.
18. Rigoni, M.: Boll. d. Soc. ital. di biol. sper. **3**:565, 1928; abstr., Ber. ü. d. ges. Physiol. u. exper. Pharmakol. **48**:584, 1929.

ance of rhythmic changes in the tone of arterial segments immersed in serum for approximately an hour. Janeway, Richardson and Park [19] observed rhythmic variations in the tone of arterial strips in Ringer-Locke solution entirely analogous to the changes described by us.

For the transient increase in tone which followed the replacement of serum by Locke's solution, we have no satisfactory explanation to offer.

Cow [9] has already described the rhythmic tonal changes occurring during the latter part of the increase in arterial tonus after the addition of serum to the chamber containing the arterial segment. He suggested that they may be responsible for the Traube-Hering blood pressure waves in the intact animal, but this seems to us unlikely.

The absence of significant quantitative differences in the tone-augmenting properties of the hypertensive and the normal serums for arterial rings speaks against the presence in the blood of patients with essential hypertension of a pressor substance acting to increase the tone of the peripheral vascular bed. The findings constitute merely a small link in the chain of negative evidence relative to this question. This becomes more apparent when certain limitations inherent in the method are considered. Thus the process of clotting may have altered or destroyed the pressor substance originally present. The effects of serums on arterial rings in vitro are not necessarily analogous to the effects on arterioles in vivo. The use of human serums and of beef arterial rings introduced an unknown factor of species difference. Furthermore, the effect of the possible pressor substance may have been overshadowed by the effect of the epinephrine-like bodies in the serum, unless the former was present in at least moderate quantities or acted to sensitize the vasoconstrictor nerve-endings to the latter. However, when considered jointly with the negative findings of Curtis, Moncrieff and Wright, Stewart, Bröking and Trendelenburg and Hülse, the results presented suggest that the pathogenesis of essential hypertension must be sought for elsewhere.

CONCLUSIONS

1. The action of thirty blood serums from patients with essential hypertension and of fifteen serums from patients with normal blood pressures on the tone of arterial segments from the mesenteric arteries of beeves was studied.

2. No significant differences were found in the vasoconstricting properties of the hypertensive and of the normal serums.

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19. Janeway, T. C.; Richardson, H. B., and Park, E. A.: Experiments on the Vasoconstrictor Action of Blood Serum, Arch. Int. Med. **21**:565 (May) 1918.

3. The results suggest that there is no peripherally acting pressor substance in the blood of patients with essential hypertension.

4. Some evidence was obtained for the residence of a spontaneous, rhythmic motor activity in arterial musculature deprived of its extrinsic innervation.

Dr. John Walker Moore rendered patients at the Louisville City Hospital and the outpatient department available for this study.

TREATMENT OF NEUROSYPHILIS

REVIEW OF RESULTS IN SIX HUNDRED AND EIGHTY PATIENTS

H. HANFORD HOPKINS, M.D.
BALTIMORE

Since the analyses of the results of treatment of patients with neurosyphilis by Stokes and Osborne (1921),[1] Fordyce (1924),[2] Stokes and Shaffer (1924)[3] and Moore (1927),[4] no similar studies dealing with large numbers of cases have been published. The accumulation of further experience with modern methods of treatment permits a report of the results obtained among 1,200 patients treated in the syphilis division of the medical clinic of the Johns Hopkins Hospital.

The clinical material on which the study is based is presented in table 1. All patients are included who on admission presented evidence of neurosyphilis or in whom it subsequently developed. The whole group of 1,199 patients was used for an estimation of the effect of previous inadequate treatment on the period of incubation of clinical neurosyphilis; the results of this study have been published.[5]

Following the practice of Head and Fearnsides,[6] Stokes and Shaffer[3] and Moore,[4] the cases were divided according to their clinical manifestations into the following groups:

1. Early neurosyphilis. The manifestations are in most instances based on purely meningeal changes, and they almost always occur within the first two years of the disease. The group includes acute syphilitic meningitis, neurorecurrence and early asymptomatic neurosyphilis.[7]

From the Syphilis Division of the Medical Clinic, the Johns Hopkins Hospital.

This investigation was supported by a grant from the Committee on Research in Syphilis, Inc.

1. Stokes, J. H., and Osborne, E. D.: Relative Effectiveness of Various Forms of Treatment in Neurosyphilis, J. A. M. A. **76**:708 (March 12) 1921.

2. Fordyce, J. A.: Results of Treatment in Syphilis of the Nervous System, Brit. J. Dermat. **36**:47 (Feb.) 1924.

3. Stokes, J. H., and Shaffer, L. W.: Results Secured by Standard Methods of Treatment in Neurosyphilis, J. A. M. A. **83**:1826 (Dec. 6) 1924.

4. Moore, J. E.: The Treatment of Central Nervous System Syphilis, J. A. M. A. **89**:588 (Aug. 20) 1927.

5. Hopkins, H. H.: The Incubation Period of Clinical Neurosyphilis, Arch. Neurol. & Psychiat. **29**:158 (Jan.) 1933.

6. Head, H., and Fearnsides, E. G.: Clinical Aspects of Syphilis of the Nervous System in the Light of the Wassermann Reactions and Treatment with Neosalvarsan, Brain **37**:1, 1914.

7. Moore, J. E., and Hopkins, H. H.: The Prognosis of Early and Late Asymptomatic Neurosyphilis, J. A. M. A. **95**:1637 (Nov. 29) 1930.

2. Diffuse late neurosyphilis. There is predominant meningeal or vascular involvement, or both, sometimes with and sometimes without parenchymatous changes. This group includes diffuse cerebrospinal syphilis and such widely separated entities as transverse myelitis, syphilitic epilepsy, gumma of the brain, combined system disease and late asymptomatic neurosyphilis.

3. Dementia paralytica and the tabetic form of dementia paralytica.

4. Tabes dorsalis.

5. Optic atrophy.

TABLE 1.—*The Material for This Study*

	Early Syphilis of Central Nervous System	Diffuse Late Syphilis of Central Nervous System	Tabes With Optic Atrophy	Tabes Without Optic Atrophy	Dementia Paralytica and Tabetic Form of Dem. Par.	Optic Atrophy Alone	Vascular Syphilis of Central Nervous System	Total
Died	6	54	13	42	71	6	8	200
Observed more than 2 years	48	187	23	88	82	35	17	480
Observed less than 2 years	65	228	34	65	75	20	32	519
Total	119	469	70	195	228	61	57	1,199

TABLE 2.—*Distribution of Cases According to Race and Sex*

	Early Syphilis of Central Nervous System	Diffuse Late Syphilis of Central Nervous System	Tabes With Optic Atrophy	Tabes Without Optic Atrophy	Dementia Paralytica and Tabetic Form of Dem. Par.	Optic Atrophy Alone	Vascular Syphilis of Central Nervous System	Total
Number of patients	119	469	70	195	228	61	57	1,199
Percentage								
White, male	42.9	34.5	55.4	63.8	65.3	32.2	31.6	47.3
White, female	11.7	14.4	4.2	16.3	15.1	9.6	3.5	10.6
Black, male	30.2	30.8	35.6	12.7	16.0	40.3	49.1	30.8
Black, female	15.1	19.6	5.6	7.1	2.6	17.8	15.8	11.9

6. Vascular neurosyphilis. In this group the disease involved only the blood vessels, so far as could be determined.

In analysis of the results, only the 480 patients who were under treatment or observation for two or more years and the 200 who died while under treatment or observation were used. The 480 patients of the former group were observed over periods varying from two to twenty years, the average period being approximately ten years.

The distribution according to race and sex is shown in table 2. The predilection of neurosyphilis for the male, especially the white male, is demonstrated again. Of particular interest are the low incidence of parenchymatous neurosyphilis (tabes and dementia paralytica) and the relatively great frequency of vascular neurosyphilis in the Negro race, whereas the distribution of diffuse meningovascular neurosyphilis is approximately equal in the two races.

Table 3 is self-explanatory, confirming the statements concerning the high percentage of asymptomatic infection in patients who develop neurosyphilis.

The much stressed importance of examining the marital partner of the patient suffering from neurosyphilis is reemphasized by the facts presented in table 4. Of 246 partners examined, more than one half were shown to be infected. The relatively greater incidence of conjugal

TABLE 3.—*Percentage of Patients Who Gave a Definite History of Primary or Secondary Syphilis*

	Early Syphilis of Central Nervous System	Diffuse Late Syphilis of Central Nervous System	Tabes With Optic Atrophy	Tabes Without Optic Atrophy	Dementia Paralytica and Tabetic Form of Dem. Par.	Optic Atrophy Alone	Vascular Syphilis of Central Nervous System	Total
Number of patients....	119	469	70	195	228	61	57	1,199
Percentage giving history.....	75.6	48.1	51.4	49.0	46.6	52.4	54.4	54.8

TABLE 4.—*Status of Marital Partner*

	Early Syphilis of Central Nervous System	Diffuse Late Syphilis of Central Nervous System	Tabes With Optic Atrophy	Tabes Without Optic Atrophy	Dementia Paralytica and Tabetic Form of Dem. Par.	Optic Atrophy Alone	Vascular Syphilis of Central Nervous System	Total
Number of patients....	119	469	70	195	228	61	57	1,199
Number of partners examined.....	15	101	10	43	63	8	6	246
Partners with syphilis of central nervous system.....	1	15	0	9	7	2	1	35
Partners with syphilis, not of central nervous system.....	8	23	0	6	4	2	1	44
Partners with syphilis, type questionable....	3	31	1	11	5	3	2	56
Partners syphilitic.....	12	69	1	26	16	7	4	135
Partners nonsyphilitic.	3	32	9	17	47	1	2	111

neurosyphilis in partners of persons with parenchymatous neurosyphilis so often reported could not be confirmed in a study of this type, the data being incomplete.

INTERPRETATION OF CHARTS

For simplification and clarity of presentation, the results of treatment have been presented in graphic form. A single chart expresses the results in a single group of cases, favorable results being charted above and unfavorable results below the middle zone, according to the schemes of treatment used. The left vertical half of each chart is

devoted to clinical results, and the right half, to serologic results;[8] at the extreme right may be seen the degree of correlation[9] between the improvement in the physical and that in the serologic status of the patient, under treatment.

The results, favorable and unfavorable, are expressed in percentages, according to six types of treatment as follows:

1. Poor treatment; that is, the patients received less than one year of treatment with the arsphenamines, heavy metals and, in a few cases, tryparsamide.

2. Routine treatment. The patients were given courses of an arsphenamine product, alternating with courses of mercury or bismuth, or both, together with large doses of potassium iodide by mouth given regularly for at least one year. Courses were usually made up of from six to eight weekly injections of the drug. The arsphenamines used were arsphenamine, neoarsphenamine and silver arsphenamine, in decreasing order of frequency.

3. Intensified routine treatment. The group given this treatment received larger doses and longer courses of the arsphenamines, in most cases, old arsphenamine. In some cases the doses were given more frequently than at weekly intervals. Courses consisted of from ten to fifteen injections. As may be seen in chart 1, this type of treatment was used almost solely for patients with early neurosyphilis.

4. Routine treatment to which was added a variable number (from three to fifteen) of intradural treatments by the Swift-Ellis method at intervals of at least two weeks. This was used mostly for the patients with tabes and those with optic atrophy.

5. Routine treatment and tryparsamide. Tryparsamide was used extensively in late neurosyphilis of all types, except in optic atrophy. It was given in doses of from 2 to 3 Gm. at weekly intervals in long courses of from ten to twenty injections. These courses were alternated with courses of bismuth or mercury and also, in some instances, with the arsphenamines.

6. Routine treatment and malaria. Malaria was used largely in the treatment of patients with dementia paralytica, but a few patients with the other types of neurosyphilis were also treated with it. Most of the

8. Only serologic results relating to the cerebrospinal fluid are considered; no attention is paid to effects of treatment on the Wassermann reaction of the blood.

9. Correlation is expressed as absolute agreement in rate per cent between the clinical and the serologic results of treatment in all the cases in which these results were excellent-excellent, fair-fair, poor-poor, expressed as percentage of the entire group. For example, if of 100 cases excellent-excellent results were obtained in 40, fair-fair in 20 and poor-poor in 20, absolute agreement between clinical and serologic results occurred in 80 per cent.

patients received routine antisyphilitic treatment and many of them tryparsamide either before or after malaria.

The legends on the charts may be defined as follows: Applied to the clinical results, "Excellent" indicates a complete disappearance of symptoms, also of signs not based on permanent degenerative changes such as Argyll Robertson pupils. "Good" means notable improvement in symptoms and signs. "Fair" means slight or no improvement. "Poor" means that the condition became worse. "Dead of Unknown Cause"

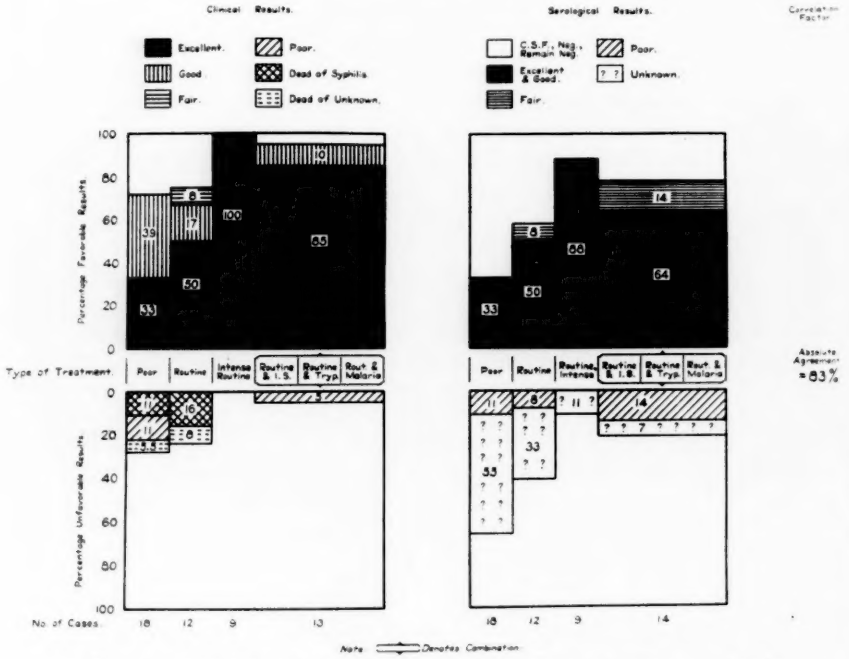

Chart 1.—Serologic and clinical results of six schemes of treatment in early neurosyphilis. The legends are defined in the text.

includes not only all the patients in whom the cause of death was unknown, but also a larger number in whom the cause of death, while known, was unrelated to syphilis. "C. S. F., Neg., Remain Neg." means that on the original examination the cerebrospinal fluid was normal and on subsequent repetition was still normal.

Applied to the serologic results, "Excellent" and "Good" mean that after treatment the spinal fluid became normal or practically so. "Fair" means that after treatment the spinal fluid showed some improvement in its previous abnormalities. "Poor" means that the abnormalities of

the spinal fluid were unaffected by treatment. "Unknown" means that the examination of the spinal fluid was not repeated.

In chart 1, dealing with early neurosyphilis, it will be seen that the best results, both clinical and serologic, were obtained with the intensified form of routine antisyphilitic treatment. The 9 patients so treated showed an excellent clinical response, and in 88 per cent there was an excellent or good serologic outcome. The degree of correlation between the clinical improvement and the serologic improvement in this group of cases was high, absolute agreement being found in 83 per cent. The figures given for the combined group of patients who received intra-

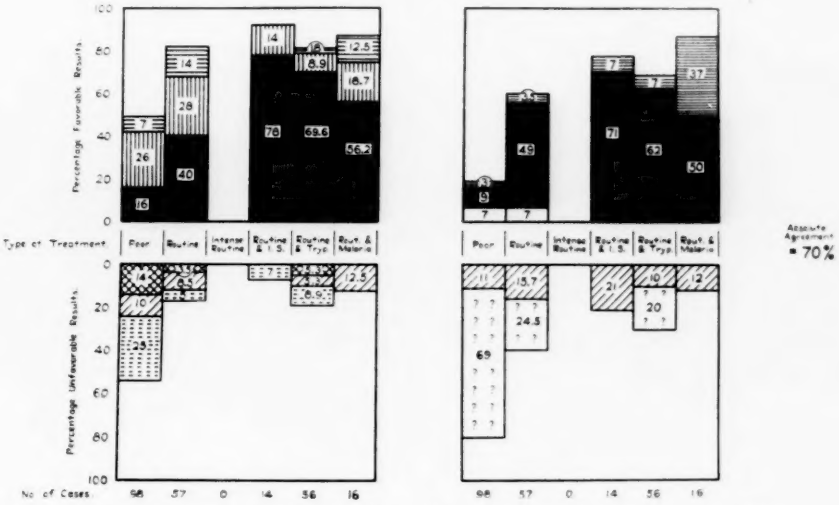

Chart 2.—The results of various types of treatment in diffuse late neurosyphilis.

spinal therapy, tryparsamide or malaria are somewhat misleading, since patients are included in this group who were resistant to previous intensive routine therapy. The fact that many patients with early neurosyphilis need more than routine treatment, however, is well demonstrated.

In chart 2, dealing with diffuse late neurosyphilis, the inadequacy of poor and even of routine treatment is clearly shown. The group who received intraspinal therapy did best (though only a small number of patients are included), and both the group receiving tryparsamide and the one receiving malarial therapy did far better than the patients who received routine treatment. In this group also, a high degree of correlation was noted between clinical and serologic improvement, absolute agreement occurring in 70 per cent.

In chart 3, illustrating the results obtained in dementia paralytica and the tabetic form of dementia paralytica, the superiority of malaria over other forms of treatment in effecting clinical improvement is striking, in spite of the fact that it had less influence on the abnormalities of the cerebrospinal fluid than did intraspinal therapy or tryparsamide.[10] The figures for malarial treatment are even more significant in the light of the fact that a number of the patients in the group treated with malaria had had all other forms of treatment before resort was had to malaria. The low incidence of deaths in the group treated with malaria as compared with that in the other groups is striking. In spite

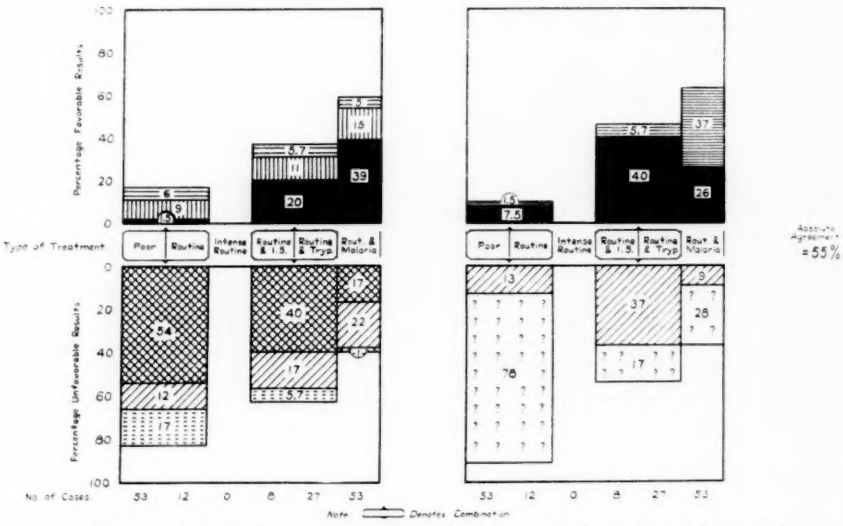

Chart 3.—The results of various types of treatment in dementia paralytica and the tabetic form of dementia paralytica.

of its preponderantly favorable clinical influence, malaria did not so frequently result in improvement in the condition of the spinal fluid. Absolute agreement was observed in only 55 per cent of the entire group with dementia paralytica. This fact is difficult of interpretation. It suggests that in parenchymatous neurosyphilis the abnormalities of the spinal fluid bear a relation to the associated pathologic changes in the central nervous system different from that in the forms of neurosyphilis which occur earlier in the life history of a person with syphilis; e. g., acute syphilitic meningitis.

10. The results in the groups receiving intraspinal and tryparsamide treatment were combined under one heading because so many of the patients received both forms of treatment. Intraspinal therapy was never given to patients with uncomplicated dementia paralytica, but only to those presenting features of tabes.

Chart 4.—The results of various types of treatment in tabes without optic atrophy.

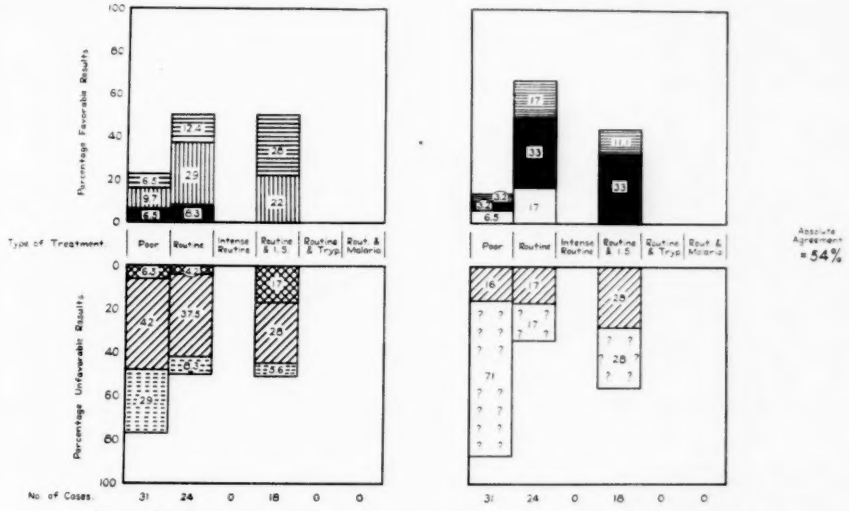

Chart 5.—The results of various types of treatment in patients with optic atrophy alone and patients with optic atrophy and tabes.

On the whole, the results of the various types of treatment in tabes were similar to those in dementia paralytica. In good clinical results obtained, intradural administration of arsphenaminized serum, treatment with tryparsamide and malarial therapy scaled upward, while in good serologic results, these therapeutic measures scaled downward. Absolute agreement occurred in only 40 per cent. The curious state of affairs observed in parenchymatous neurosyphilis is thus even more striking in tabes than in dementia paralytica. Although the number of tabetic patients treated with malaria was small, the high degree of clinical success obtained with this type of therapy augurs well for its more widespread use.

The results of treatment in the group with optic atrophy are expressed as of optic atrophy alone. Without explanation, the chart gives a false impression of what may be accomplished in this most dreaded complication. The apparent superiority of routine and even of poor treatment shown by the chart is due to the fact that the group treated by the Swift-Ellis method contained those patients in whom optic atrophy progressed in spite of previous antisyphilitic treatment. Thus the 22 per cent good results in the group receiving intraspinal treatment represent slight improvement, and the 28 per cent fair results, arrest in previously progressive atrophy. A detailed analysis of this group of cases appears in a recent paper by Moore.[11]

The number of patients with purely vascular neurosyphilis was so small that no attempt was made to analyze the results in detail. There were only 8 patients who died while under observation and 17 who were observed for periods longer than two years. In general, treatment accomplished comparatively little in the return of function after paralysis had occurred.

SUMMARY AND CONCLUSIONS

A study of about 1,200 patients with various forms of neurosyphilis, 200 of whom died while under observation and 480 of whom were observed for more than two years before lapsing, is reported. The percentage of patients who gave a history of early syphilis, the distribution according to race and sex and the status of the marital partners among this group are given. The results of treatment are presented in graphic form according to seven clinical groups of neurosyphilis and six schemes of treatment. The comparative results of treatment under the six plans warrant the following conclusions:

1. In early neurosyphilis the best method of treatment, in our experience, was an intensified form of routine antisyphilitic treatment with arsphenamine.

11. Moore, J. E.: The Syphilitic Optic Atrophies, Medicine **11**:263 (Sept.) 1932.

2. In diffuse late neurosyphilis routine antisyphilitic treatment was much inferior to treatment with arsphenaminized serum subdurally administered, tryparsamide or malaria. The serum gave the best results, but tryparsamide gave almost as good, and owing to the much larger number of patients treated with it, the results probably represent a more nearly exact comparative estimation of its value.

3. In dementia paralytica and the tabetic form of dementia paralytica, malaria was preeminently the treatment of choice.

4. In tabes, the best results were obtained with malaria, although those receiving tryparsamide did almost as well, and both types of therapy were far superior to routine treatment.

5. In optic atrophy, treatment with subdural injections of arsphenaminized serum was successful in arresting the process in numerous cases in which it was advancing in spite of routine methods of treatment.

6. The number of patients with purely vascular neurosyphilis was too small for statistical analysis.

7. In general, the correlation between the clinical and the serologic improvement is roughly proportional to the duration and type of pathologic involvement. In early neurosyphilis, absolute agreement is found in a high percentage, and in parenchymatous neurosyphilis in a correspondingly low percentage, of patients under treatment.

HYPERINSULINISM

REPORT OF A CASE OF SPONTANEOUS HYPOGLYCEMIA, WITH STUDIES IN DEXTROSE TOLERANCE

EUGENE ZISKIND, M.D.*

LOS ANGELES

Spontaneous hypoglycemia is being reported with increasing frequency. The subject was recently reviewed by Gammon and Tenery.[1] The record of a patient who has been under observation for one year follows.

REPORT OF A CASE

History.—A youth, aged 19, a student, was admitted in a state of coma to the Los Angeles County General Hospital on Sept. 8, 1930. For eighteen months prior to admission he had had spells of weakness, headache, trembling and mental confusion occurring at about noon. These the patient attributed to waiting until 1 o'clock for his midday meal. Eating relieved the symptoms. During the eighteen months the patient's weight had increased from 128 to 141 pounds (58 to 64 Kg.). He had not engaged in athletics for one year, because excessive perspiration and a feeling of weakness readily developed on exertion. On September 2, he complained that his mind was a "blank." Three days later he suffered from headache and dizziness. On September 6, he had a series of convulsions involving the right arm and leg, and was semistuporous until 5 p. m. On the next day he had another convulsion, and he remained in coma.

Birth was by forceps delivery. Harelip and cleft palate were repaired at 4 months, and again at 3 years of age. The patient had pneumonia with a convulsion at 2 years; later in childhood he had chickenpox, scarlet fever, measles and influenza with delirium lasting thirty-six hours. There had been many infections of the upper respiratory tract, but none in the last five years. The family history was irrelevant.

Physical Examination.—The patient, well developed and well nourished, was in coma. The temperature was 102 F.; the pulse rate, 108, and the respiratory rate, 22. The blood pressure registered 120 systolic and 85 diastolic. Except for the harelip, cleft palate and external hemorrhoids, examination of the head, neck, heart, lungs and abdomen revealed no abnormality. There was right hemiparesis, with hyperactive deep reflexes and a positive Babinski sign on the same side.

Laboratory Reports.—No urine was obtained on catheterization, but the blood sugar was 40 mg. per hundred cubic centimeters on two determinations by the

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* Instructor in neurology, Medical School, University of Southern California.

From the neurologic services of the late Dr. I. L. Meyers and Dr. S. D. Ingham, the Los Angeles County General Hospital.

1. Gammon, G. D., and Tenery, W. C.: Hypoglycemia: Clinical Syndrome, Etiology and Treatment: Report of Case Due to Hyperinsulinism, Arch. Int. Med. **47**:829 (June) 1931.

Benedict method.[2] A specimen of urine obtained a few hours later was straw-colored and acid, with a specific gravity of 1.037, and showed albumin, 4 plus; acetone, 2 plus; no sugar, no blood, and many pus cells, with an occasional granular cast. The red blood count was 4,870,000; the white blood count, 11,480, with 67 per cent polymorphonuclear neutrophils, 17 per cent small lymphocytes, 2 per cent large lymphocytes, 7 per cent transitional cells, 3 per cent basophils and 1 per cent eosinophils, and hemoglobin, 97 per cent (Sahli). Examination of the spinal fluid revealed 3 cells per cubic millimeter, a trace of globulin, a normal amount of sugar (rough test) and negative Wassermann, Kahn and colloidal benzoin tests.

No definite diagnosis was made. The day after admission (Sept 9), the patient was transferred to the neurologic service of Dr. I. L. Meyers, still in coma, with a complete right-sided hemiparesis, an inconstant Babinski sign on the left and slight blurring of the nasal margins of both optic disks. The results of the remainder of the neurologic examination were unimportant. The blood sugar was 58 mg. per hundred cubic centimeters; the carbon dioxide combining power, 69 per cent by volume; nonprotein nitrogen, 35 mg., and creatinine, 1.4 mg. Subsequent urinalyses, phenolsulphonphthalein and Mosenthal tests gave negative results. Since the blood sugar was still very low, despite the administration of 150 Gm. of dextrose in the intervening twenty-four hours, I suggested that the coma was probably dependent on the hypoglycemia.

Numerous tests to determine the cause of the hypoglycemia were performed. On the whole, these gave negative results. Spinal puncture (Sept. 16, 1930) gave initial pressure, 160 mm.; no block, 4 cells and no globulin. On Sept. 19, 1930, the findings were the same, except that the pressure was 200 mm. The Wassermann and Kahn tests of both the blood and the spinal fluid were negative. Roentgenograms of the skull on Sept. 11, 1930, and on June 8, 1931, revealed no abnormality. Injections of epinephrine produced a rise in the blood sugar (table 1). The basal metabolic rates were normal:

1931	Basal Metabolic Rate	Blood Sugar
June 11	minus 24	63
June 13	plus 8	56
June 17, 8 a. m.	minus 2	57
June 17, 9 a. m.	plus 8	51
June 17, 10 a. m.	minus 1	53
June 19	minus 4	62

Van den Bergh reactions (direct and indirect), icteric index and determinations of blood calcium (serum and diffusible) were all within normal limits. Blood serum tension, unheated,[3] was 40 dynes per cubic millimeter; heated, 47 dynes per cubic millimeter. Schmidt test meal for external pancreatic function was normal. Roentgenograms of the long bones, chest, gastro-intestinal tract and gallbladder showed that these were normal. A test meal of 70 Gm. protein (cottage cheese and egg white) gave the following blood sugar curve: fasting, 71 mg.; after half an hour, 69 mg.; after one hour and a half, 83 mg.; after two hours and a half,

2. Benedict, Stanley R.: The Estimation of Sugar in Blood and Normal Urine, J. Biol. Chem. **68**:759 (June) 1926.

3. Lovell, C.: Surface Tension of Serum in Anxiety Psychoses, J. Ment. Sc. **69**:397 (Oct.) 1923. Farran, R. C., and Drury, K. K.: Types of Blood Sugar Curve Found in Different Forms of Insanity, ibid. **71**:8 (Jan.) 1925.

83 mg., and after three hours and a half, 64 mg. The blood sugar curve following the oral administration of 100 Gm. of fat (butter and oil emulsion) was: fasting, 56 mg.; after one hour, 58 mg.; after two hours, 53 mg.; after three hours, 52 mg., and after three hours and a half, 122 mg.[3a] A test meal of raw starch (Rosenthal)[4] produced a slight rise in the blood sugar. Attempts to feed a diet low in carbohydrates was unsuccessful because of the frequent hypoglycemic reactions.

The minimal carbohydrate requirement for three days in March, 1931, varied from 474 to 536 Gm., approximately, for each day. This exceeded the amount (360 Gm.) designated by Allan as necessary to compensate for complete loss of function of the liver.[5]

TABLE 1.—*Reactions to Epinephrine*

Date	Amount of Epinephrine 1 to 1,000, Minims	Before Injection		During Injection, Blood Sugar	After Injection	
		Time, Minutes	Blood Sugar		Time, Minutes	Blood Sugar
11/18/30	10	20	83	87	10	90
		10	87		20	109
					30	110
1/ 5/31	10	10	68	72	10	82
					20	114
					30	104
3/21/31*	15	10	66	..	5	66
					20	77
					35	93
					50	90
6/25/31	15	5	73	..	60	105

* Breakfast was eaten at 7:45 a. m. All other tests were taken at least four hours after the last feeding (orange juice).

TABLE 2.—*Metabolic Rates During Dextrose Tolerance Tests*

Date	Test	Fasting	Time After Administration of Dextrose			
			1 Hour	2 Hours	3 Hours	4 Hours
6/13/31	Basal metabolic rate	+8	+41	+21	+19	−24
	Blood sugar	56	133	164	91	57*
6/17/31	Control, basal metabolic rate	−2	+8	+1		
	Control, blood sugar	57	51	53		
6/18/31	Basal metabolic rate	−4	+29	+23	+13	+4
	Blood sugar	62	129	128	51	55

* The patient was very restless.

The effect of dextrose on the metabolic rate is shown in table 2.

None of these tests aided in the elucidation of the etiologic factor for the hypoglycemia.

Course.—For the first ten days of hospitalization, the patient was in a coma of fluctuating depth. During this period the variability of the neurologic findings was remarkable. Hemiparesis and some degree of coma were the most constant,

3a. A convulsion occurred after the third hourly specimen.

4. Rosenthal, S. F.: Pancreatic Function and Upper Intestinal Digestion, Arch. Int. Med. **41**:867 (June) 1928.

5. Allan, F. N.: Hyperinsulinism: Report of Two Cases, Arch. Int. Med. **44**:65 (July) 1929.

and were present at every examination. The Babinski response was present or absent, unilaterally or bilaterally. Rigidity of the neck was inconstant, and the excitability of the tendon reflexes varied. Once there were definite catatonic features. The changing signs were not unlike the picture of cerebral edema so often seen in uremia or eclampsia. In this instance, however, it was probable that the variability of the symptoms was associated with fluctuations in the blood sugar level.

The patient received frequent feedings of dextrose or orange juice by vein and nasal tube. Numerous blood sugar determinations taken just before feedings varied from 50 to 60 mg. On September 19 rigid attempts were first made to keep the blood sugar above hypoglycemic levels at all times during the twenty-four hours. It was calculated that 350 cc. of 10 per cent dextrose administered intravenously at six hour intervals would accomplish this object. Concomitantly, the patient roused to consciousness. It now became apparent that he had aphasia. He was definitely apraxic for a few days. On September 29, there could be demonstrated an anomial aphasia, with some tendency to perseveration. On October 1, the patient was able to cooperate in an examination of the visual fields;

TABLE 3.—*Blood Sugar Readings for Nov. 5, 1930*

Time	Blood Sugar	Comment
8:37 a.m.	76	Headache
9:37	97	Breakfast at 9:30 a. m.
10:37	96	
11:37	105	
12:37 p.m.	77	Headache
1:50	67	Generalized perspiration; tremor of hands; slight weakness of right arm
2:50	65	Restlessness
4:00	61	Pupils dilated; ataxia and tremor more marked, especially on the right; headache intense, greater restlessness
5:00	60	Drowsy; slight headache
6:10	52	Comatose; readily roused

Neurologic examination yielded no findings other than those noted, except the residual visual field defect and the absence of the plantar reflex on the right, which remained unaltered throughout.

he had a right homonymous hemianopia. The diagnosis of a vascular lesion was made; this was probably a thrombosis involving the cortex in the region of the angular gyrus. It was assumed that the lesion was secondary to the hypoglycemia. All the neurologic symptoms showed progressive improvement. The hemiparesis disappeared first, and on October 25, practically all the aphasia was gone. The visual defect cleared slowly; it was eleven months before the fields were again normal.

After the patient regained consciousness, feedings were given by mouth at frequent intervals. His appetite was great. He ate two or three trays of food at each meal and often ate between meals. When the feeding at 2 a. m. was omitted, the patient became mentally disturbed. Once he walked down the fire escape, apparently asleep. At another time, he walked to the center of the ward and urinated on the floor. In the morning, he would deny all knowledge of these episodes.

When recovery from the neurologic symptoms was well advanced, the effect of withholding food was tested. On Nov. 5, 1930, after a light breakfast at 9:30 a. m., the blood sugar level was determined every hour (table 3). When the blood sugar was 52 mg., dextrose was given, since I did not wish to hazard loss of consciousness. Again, on November 22, the patient received no breakfast,

and a blood sugar determination, taken at 10 a. m., was 54 mg. In less than an hour he had a convulsion. It was apparent that the tendency to hypoglycemia still persisted.

The patient was discharged to the outpatient department on Nov. 26, 1930, at which time the only neurologic abnormality was a moderate visual field defect. He was readmitted to the hospital on Nov. 26, 1930, after a convulsion due to the omission of orange juice in the morning.

Since the hypoglycemic tendency was not improving, an abdominal operation was performed by Dr. Walter Bayley on March 26, 1931, in the hope of finding a tumor of the pancreatic islets. At operation, the pancreas was found to be comma-shaped, but normal in appearance and consistency. No tumor mass was seen or felt. The liver was smooth and of normal color and consistency. No tumor was palpated in the region of the suprarenal glands. It had previously been decided to remove about three fourths of the pancreas if no tumor was discovered.[6] Technical difficulty was encountered in that the splenic vein ran through the pancreatic tissue so that very little of the organ could be removed without sacrificing the spleen. Therefore, only 7.2 Gm. of the tail of the pancreas was excised. No abnormalities could be detected in this tissue microscopically. Measurements of the size of the islets were normal. Physiologic assay, which was performed by Dr. D. A. Scott of the University of Toronto, showed that the tissue had "only about one-tenth the amount of insulin present in the pancreas from other sources." The low figure was attributed to deterioration in the acid alcohol. Although fixed in the latter according to instructions previously received from Dr. Scott, the tissue was not sent to Canada until twenty-four days later. Hence this physiologic assay may show far from the actual amount of insulin originally present in the tissue.

As was to be expected, little or no improvement resulted from the operation.

Thyroid Therapy.—Since operation failed to effect a cure, it was thought advisable to try the use of certain endocrine products. Because of the apparent antagonism between thyroid secretion and insulin, as shown by the diminished effect of insulin in diabetic patients having hyperthyroidism, thyroid extract was decided on. Janney and Henderson[7] have indicated that hypothyroid conditions are associated with increased tolerance for dextrose, and hyperthyroid states with diminished tolerance. Wagner and Parnas[8] reported that the blood sugar of their patient could be restored to normal by therapy with thyroid.

It should be recalled that my patient presented none of the classic signs of thyroid disease, and the basal metabolic rate was normal. Thyroid, 1 grain (0.06 Gm.) was administered daily by mouth, the dose being increased 1 grain each day. When the patient was taking 34 grains a day (2.2 Gm.), the weight had fallen from 151 to 143 pounds (69 to 65 Kg.), and the metabolic rate had risen to + 52. The treatment was discontinued. The blood sugar level was not materially affected by the medication with thyroid. It may be that any tendency of the thyroid to elevate the blood sugar was counterbalanced by the increased utilization of dextrose incident to the rising metabolic rate.

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6. Finney, J. M. T., and Finney, J. M. T., Jr.: Resection of the Pancreas, Ann. Surg. **88**:584 (Sept.) 1928. Allan, F. N.; Boeck, W. C., and Judd, E. S.: The Surgical Treatment of Hyperinsulinism, J. A. M. A. **94**:1116 (April 12) 1930.

7. Janney, N. W., and Henderson, H. E.: Concerning the Diagnosis and Treatment of Hypothyroidism, Arch. Int. Med. **26**:297 (Sept.) 1920.

8. Wagner, R., and Parnas, J. K.: Ueber die Phasen des Kohlehydratumbaues nach Versuchen, die an einem Fall besonderer Kohlehydratstoffwechselstörung angestellt wurden: I, Ztschr. f. d. ges. exper. Med. **25**:361, 1921.

Daily injections of an anterior lobe pituitary preparation, 1 cc. daily for a short period, was given because of Wilder's [9] assumption that some instances of spontaneous hypoglycemia are due to deficiency of the anterior pituitary lobe. No improvement was noted, though the drug was not given a long time.

At the end of one year the condition of the patient remained essentially unaltered. There have been ample demonstrations of the hypoglycemic tendency, but control has been easy and reactions occurred chiefly when the frequent feedings were omitted, accidentally or for various tests. The patient was told to eat all he wanted and to have food between meals, and throughout the entire period he was usually awakened for orange juice or egg-nog once or twice during the night. He learned to appreciate signs of oncoming reactions and to ask for orange juice. These attacks were as readily overcome as those of overdosage of insulin. The most frequent premonitory sign was a tingling or numbness of the right hand. In attacks he would present many of the signs noted early after admission, e. g., variations in the Babinski response and tendencies to anomia and perseveration, as well as convulsions and coma. Dilatation of the pupils, excessive perspiration and tremor of the hands were early and almost constant phenomena during attacks. Twice when blood sugar readings were available shortly before and after convulsions, a definite rise in the blood sugar from the hypoglycemic level to normal was noted as a result of the seizure. Only on occasions of hypoglycemia did seizures occur.

Neurologic examinations between attacks gave entirely negative results, except for a persistent defect of the visual field, which was decreasing gradually. When tested on Sept. 16, 1931, the visual fields were normal.

The patient's condition, so far as the hypoglycemic tendency is concerned, is almost the same as it has been for nine months. Since omission of thyroid therapy, his weight has increased to 160 pounds (73 Kg.).

COMMENT

The coma, hemiparesis, aphasia and hemianopia, all of which underwent a gradual resolution, indicated a cerebral vascular lesion. The onset of these symptoms during a period of hypoglycemia and their tendency to recur in subsequent hypoglycemic spells suggest that the cerebral lesion was secondary to the lowered blood sugar.

The neurologic symptoms persisted for an unusually long time. Following administration of insulin and in cases of hyperinsulinism, transient nervous phenomena are common. Persisting neurologic manitendency to recur in subsequent hypoglycemic spells suggest that the Ravid [10] reported hemiplegia of three and seven hours' duration after injections of insulin. He also stated that Joslin had seen two patients in whom the paralysis lasted a few days and a few weeks respectively. Hence it is not altogether surprising that in prolonged hypoglycemic states, such as may occur in patients with hyperinsulinism, neurologic

9. Wilder, J.: Ein neues hypophysares Krankheitsbild: Die hypophysare spontanhypoglykämie, Deutsche Ztschr. f. Nervenk. **112**:192 (May) 1930.

10. Ravid, J. M.: Transient Insulin Hypoglycemia Hemiplegias, Am. J. M. Sc. **175**:756 (June) 1928.

symptoms of long duration may occur. This apparently was the case with my patient.

Of interest are the observations in cases in which a blood sugar determination was secured immediately before and shortly after a convulsion. A postconvulsive rise in the blood sugar to normal or higher levels was demonstrated. This homeostatic significance of hypoglycemic convulsions has been commented on before.

Despite extensive investigations of the endocrine glands, no etiologic factor was found to explain the low blood sugar in this patient. It is, of course, possible that there is an adenoma of the pancreas so situated as to have escaped observation at operation.

STUDIES IN TOLERANCE OF DEXTROSE

Diabetes mellitus and hyperinsulinism presumably represent opposite secretory states of the pancreatic islets: the former, hypo-activity, and the latter, hyperactivity. In diabetes, hypo-insulinism, there is a decreased tolerance for carbohydrates. In hyperinsulinism one would therefore expect an increased tolerance.[11] However, in most of the cases of lesions in the pancreas or liver the dextrose tolerance curves were similar to those seen in diabetes (table 4). The explanation of this striking fact attracted my attention. Very little discussion on this subject is to be found in the literature. The attitude usually expressed is that a perverted pancreatic secretion, dysinsulinism, is present. Wilder and others [12] found at necropsy an excessive amount of glycogen in the liver of their patient. Hence they interpreted the curves showing a prolonged high blood sugar as being due to inability of the liver to store more sugar, since its glycogen capacity was saturated. Wagner and Parnas [8] assumed that there existed a disturbance of the normal storing capacity of the liver for dextrose. They thought, however, that it was the glycogen-storing function of the liver that was primarily impaired, so that the amount of glycogen in the liver was less than normal.

In view of the conformity of the rest of the clinical picture to that which might be expected in true hyperinsulinism, the value of the dextrose test by mouth as an index of tolerance was questioned. Variations in the rate and degree of absorption of dextrose from the intestinal tract might influence the test [13] and thus introduce an error in the

11. Harris, Seale: Hyperinsulinism and Dysinsulinism, J. A. M. A. **83**:739 (Sept. 6) 1924.

12. Wilder, R. M.; Allan, F. N.; Power, M. H., and Robertson, E. A.: Carcinoma of the Islands of Pancreas; Hyperinsulinism and Hypoglycemia, J. A. M. A. **89**:348 (July 30) 1927.

13. Beeler, C.; Bryan, A. W.; Cathart, E. P., and Fitz, R.: An Improved Alimentary Glucose Tolerance Test, J. M. Research **1**:549, 1922.

interpretation of dextrose tolerance. This has been vigorously denied.[14] It was nevertheless decided to rule out this possibility by an intravenous test.

Following the technic used by Lennox and Bellinger [15] (0.3 Gm. of dextrose per kilogram of body weight in a 20 per cent solution

TABLE 4.—*Dextrose Tolerance Curves in Cases of Hyperinsulinism*

Author		Fasting	Time After Administration of Dextrose: ½ Hour	1 Hour	2 Hours	3 Hours	4 Hours
Carr et al.: J. A. M. A. (February 7) **96**: 1363 (Apr. 25) 1931	(March 18)	81	134	132	135	102	
		81	161	172	119	101	62
Finney and Finney [6]		79	232	196	192		
		52	192	...	135*	111†	
Howland et al.: Carcinoma of Pancreas, J. A. M. A. **93**: 674 (Aug. 31) 1929		80	160	230	260	240	
Nadler and Wolfer: Carcinoma of Liver, Arch. Int. Med. **44**: 700 (Nov.) 1929		45	...	209	206	158	
Wilder et al.: Carcinoma of Pancreas [13]		68	242	283	223	70	
Womack et al.: J. A. M. A. **97**: 631 (Sept. 19) 1931		100	175	210	170	165†	
Ziskind	9/11/30	51.9	109	166	222		
	11/12/30	77	144	144	157		
	11/20/30	65	114	116	122	76	63
	1/ 8/31	58	133	120	142	93	59
	4/ 3/31	75	183	232	141	94	
	6/13/31	56	...	133	164	91	57
	6/19/31	62	...	129	128	51	43

* 1½ hours.
† 2½ hours.

TABLE 5.—*Intravenous Dextrose Tolerance Tests*

Author	Date	Fasting	Time After: 4 Min.	15 Min.	30 Min.	45 Min.	60 Min.	2 Hr.
Ziskind	3/16/31	51	303	146	99	78	66	
	3/24/31	65	222	194	160	65	60	65
	4/11/31	70	202	133	...	87	70	54
Lennox (average normal)	.....	100	222	150	120	90	95	
Control	4/11/31	142	185	191	157	131	112	76

administered over a period of four minutes), a number of intravenous tests were made on the patient. The results (table 5) did not show a

14. Joslin, E. P.: The Treatment of Diabetes, Philadelphia, Lea & Febiger, 1928, p. 200.

15. Lennox, W. G., and Bellinger, M.: Comparison of Blood Sugar Curves Following Ingestion and Intravenous Injection of Glucose, Arch. Int. Med. **40**:182 (Aug.) 1927.

definitely decreased tolerance as compared with the intravenous curves of Rigler [16] in diabetes; neither did they suggest increased tolerance.

The continuous intravenous method of Woodyatt [17] for determining tolerance for dextrose was employed next. This I believe to be the most accurate known means of measuring the tolerance for dextrose. Woodyatt states that tolerance for dextrose depends on the rate at which the tissues are able to abstract a known amount of dextrose from the blood by their combined powers to burn it, to reduce it into fat or to polymerize it into glycogen, and should be expressed as a velocity in grams of dextrose abstracted from the circulation for each kilogram of body weight for a unit of time. Woodyatt found the normal tolerance to be 0.8 Gm. of dextrose per kilogram of body weight during an hour. When dextrose was administered continously by vein by means of the Woodyatt pump, the figures obtained for the patient whose case has been reported were approximately 1.3 Gm. per kilogram of body

TABLE 6.—*Results with Woodyatt Dextrose Pump*

Time	Amount 20 per Cent Dextrose per Hour, Cc.	Dextrose per Kg. of Body Weight per Hour, Gm.	Blood Sugar	Urinary Sugar, per Cent
Fasting	...	...	57	
7:00 to 7:30 a.m.	200	0.7	119	0
7:30 to 8:00	240	0.8	158	0
8:00 to 8:30	312	1.0	186	0
8:30 to 9:00	400	1.3	256	0.5

weight an hour (table 6). This represented an increased tolerance of 63 per cent and is more consistent with the type of tolerance to be expected in hyperinsulinism. If similar results are obtained in other cases, the dextrose test by mouth should be discarded as a true index of tolerance, and the presence of an increased tolerance in hyperinsulinism should be accepted as a fact.

The explanation for the different curves obtained by the intravenous and oral methods, though possibly bound up with the question of intestinal absorption, is not clear. Beeler and others [13] showed that when the dextrose was administered orally, from 22 to 68 per cent could be aspirated from the stomach at the end of the first hour. In the case reported in this article aspiration of the stomach contents

16. Rigler, L. G., and Ulrich, H. L.: Blood Sugar Reaction Following Intravenous Injection of Glucose, Arch. Int. Med. **32**:343 (Sept.) 1923.

17. Woodyatt, R. T.; Sansum, W. D., and Wilder, R. M.: Prolonged and Accurately Timed Intravenous Injections of Sugar, J. A. M. A. **65**:2067 (Dec. 11) 1915; The Method of Timed Intravenous Injections, J. Biol. Chem. **25**:355 (March) 1917.

one hour after the dextrose was given resulted in a marked fall in the blood sugar, but this also happened subsequently in controls (without aspiration). In control tests hyperglycemia did not follow the ingestion of sugar; this can possibly be explained on the basis of overstimulation of the insulin-secreting mechanism by repeated dextrose tests.[18]

SUMMARY

1. A case of spontaneous hypoglycemia is presented, with observations over a period of one year. This case is unique in that a cerebral vascular lesion presumably due to the hypoglycemia was present and persisted for a long time.

2. No abnormality in the pancreas was noted at operation. Clinical investigation of the endocrine glands did not reveal a causative agent for the hypoglycemia.

3. No improvement resulted from therapy with thyroid.

4. An increased tolerance for carbohydrate was revealed by the intravenous dextrose test of Woodyatt, whereas the oral dextrose test indicated a decreased tolerance. In view of the greater validity of the Woodyatt test, the increased tolerance shown by this test may represent the true state of carbohydrate tolerance in these cases.

In the study of this case, the author has availed himself freely of all the facilities for consultation and of the cooperation of the various specialty departments at the Los Angeles County General Hospital. Dr. Newton Evans, pathologist at the hospital, secured for me the cooperation of the laboratory. Mrs. R. Bolton made assiduous efforts in securing basal metabolic rates on a patient with harelip. Dr. A. Chaney, hospital chemist, and Miss L. Giebelstein, dietitian, assisted in the management of this case.

1930 Wilshire Boulevard.

18. Lennox, W. F.: Stimulation of the Sugar-Regulating Mechanism as Shown by Duplicate Blood Sugar Curves, J. Biol. Chem. **73**:237, 1927.

BLOOD CHOLESTEROL IN THYROID DISEASE

II. EFFECT OF TREATMENT

LEWIS M. HURXTHAL, M.D.
BOSTON

In part I of this study, the blood cholesterol values found in different types of thyroid disease were presented. This report deals with the effect of preoperative and operative treatment. The cases dealt with herein comprise those in which postoperative myxedema did not occur. Cases in which myxedema did occur will be dealt with in part III of this study. On the other hand, cases with postoperative low metabolic rates but without clinical evidences of low thyroid function are included.

EFFECT OF PREOPERATIVE AND OPERATIVE TREATMENT

Effect of Preoperative Treatment in Exophthalmic Goiter.—It was shown in part I that patients who had received iodine before coming under observation had a higher average value for cholesterol and a lower average basal metabolic rate than those who had not. Preoperative preparation, which consisted mainly of the administration of 30 minims (1.9 cc.) of compound solution of iodine daily, an adequate amount of fluid and a high caloric diet, was carried on from six to fourteen days. As a rule, a second basal metabolic rate was taken on the sixth day, at which time the blood was taken for cholesterol analysis. In table 1 are shown the results in sixty-eight cases of exophthalmic goiter, in which one-half of the patients had received iodine before admission to the hospital and one-half had not. The effect of preoperative treatment was, on the whole, greater in the latter group, as shown by the lowering of the basal metabolic rate and the elevation of the blood cholesterol.

That patients improve more rapidly when they have not received iodine before preoperative iodinization has been noted by many on clinical observation and on study of the basal metabolic rate. Confirmation of this by cholesterol studies is of interest.

Effect of Preoperative Regimen of Iodine on Toxic Adenomatous Goiter.—The effect of compound solution of iodine was noted in eight cases; the average values are shown in table 2. There was an increase in cholesterol in every case but two, in both of which compound solution

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From the Medical Department of the Lahey Clinic and the Chemical Laboratories of the New England Deaconess Hospital.

of iodine had been given for only a few days and in one of which the condition was complicated by diabetes mellitus.

Immediate Effect of Hemithyroidectomy or Subtotal Thyroidectomy.—The data illustrating the effect of operation are given in detail in tables 3 and 4. The averages are shown in charts 1 and 2. It will be

TABLE 1.—*Effect of Preoperative Treatment on Level of Blood Cholesterol in Exophthalmic Goiter*

	Before Treatment				After Treatment			
	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.
A. Patients with history of iodine administration before admission to hospital; average in 34 cases	45.3	104.0	124.9	127.0	33.4	96.6	125.8	141.8
B. Patients without history of iodine administration before admission to hospital; average in 34 cases	55.0	105.0	122.2	123.5	32.0	93.2	124.4	144.0

TABLE 2.—*Toxic Adenomatous Goiter: Results of Preoperative Treatment (Iodine) in Eight Cases*

		Before Treatment				After Treatment			
Days of Treatment	Number	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.
10	1	40	104	122	122	21	84	122	207
4	2	87	152	134	132	63	128	135	165
5	3	17	72	115	156	5	66	118	172
5	4	50	104	108	121	36	104	104	148
5	5	30	118	155	125	27	112	150	149
4	6	80	144	112	158	62	136	110	148
5	7	26	98	113	152	28	80	114	150
10	8	Too sick to take B.M.R.			88	27	86	113	143
Total		330	792	859	1,054	269	796	966	1,282
Average		47	113	123	132	34	99	121	160

noted that six days after operation there is an average rise of the cholesterol content over that before operation. There are exceptions; because of postoperative thyroid and febrile reactions, some patients may show a marked drop in the cholesterol content of the blood. At this point of observation there is less correlation between the cholesterol value and the basal metabolic rate than at any other time. Infection tends to lower the cholesterol value, as will be shown later.

Values at Intervals of from Three to Twelve Months After Operation.—In tables 3 and 4 are shown values obtained at various intervals

TABLE 3.—*Cholesterol Content of the Bl*

Line Number	Date	Sex	Age	Duration, Months	Weight Loss in Pounds	Iodine Before Admission	On Admission to Hospital: Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	Before Operation: Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	Six Days After Oper: Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds
1	4/15/31	F	18	..	5	+	25	126	113.5	93	19	120	117.0	128	14	94	113.5
2	5/12/31	F	33	12	15	+	50	118	143.7	94	38	86	144.5	117	24	80	141.0
3	4/27/31	F	39	12	18	+	31	96	112.0	101	34	102	112.7	136	21	88	109.0
4	5/19/31	M	50	24	27	0	48	90	134.7	102	10	89	134.5	124	6	76	133.0
5	3/16/31	F	43	12	10	0	37	98	100.2	156	21	92	104.0	105	16	104	102.0
6	6/18/31	F	24	2	15	0	62	110	109.0	132	2	86	111.5	182	3	70	108.0
7	3/24/31	M	36	3	3	+	13	76	155.0	104	2	76	158.0	177	13	79	153.0
8	5/14/31	F	21	?	3	+	47	100	106.7	110	19	84	107.2	129	4	80	106.0
9	6/ 2/31	M	24	?	6	+	45	108	122.0	138	47	88	123.7	119	11	100	123.0
10	3/24/31	M	29	24	40	..	30	76	155.0	119	11	98	162.0	175	0	72	179.0
11	5/ 4/31	F	46	6	10	+	44	118	116.0	102	24	110	111.7	120	−6	76	125.0
12	6/ 1/31	F	19	12	6	0	49	100	111.5	117	53	116	112.0	159	2	80	113.0
13	5/29/31	F	20	12	4	0	41	99	108.7	149	28	92	111.0	143	7	78	108.5
14	5/19/31	F	37	8	10	+	29	86	120.5	133	37	94	124.0	114	13	88	116.0
15	4/13/31	F	42	3	31	+	34	108	101.0	176	38	112	102.0	168	16	90	100.5
16	5/28/31	F	45	?	0	+	34	110	128.7	98	31	112	130.0	122	27	122	125.0
17	4/26/21	F	30	..	12	0	67	96	126.0	121	34	94	129.5	182	21	88	125.0
18	6/ 9/31	M	38	12	36	0	38	94	133.0	134	8	84	138.7	152	10	94	137.0
19	1/26/31	F	49	4	34	0	44	94	95.5	105	33	80	93.7	154	10	86	94.5
20	2/19/31	F	21	..	6	0	35	114	124.5	150	48	86	122.5	159	9	110	120.0
21	6/ 6/31	F	20	3	5	+	27	98	110.0	149	24	96	113.7	142	29	80	110.0
22	2/17/31	F	43	3	10	+	51	112	117.0	121	22	96	119.5	187	..	...	.....
23	4/ 9/31	F	33	..	7	+	31	90	103.0	174	25	120	103.0	212	9	96	104.0
24	6/ 2/31	M	34	..	..	+	65	108	150.0	99	45	94	157.0	114	..	...	.....
25	4/ 1/31	F	37	9	23	+	37	100	136.0	111	..	...	.....	...	8	92	125.0
Total.....			831	159	336		1,014	2,525	3,033.2	3,088	653	2,307	2,943.4	3,520	267	2,023	2,751.0
Average.....			33.2	9.3	14		40.5	101	121.3	123.5	27.2	96.1	122.6	146.6	11.6	87.9	119.6

TABLE 4.—*Effect of Two-Stage Opera*

Line Number	Date	Sex	Age	Duration, Months	Weight Loss in Pounds	Iodine Before Admission	On Admission: Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	Before First Operation: Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	After First Operation Before Second Oper: Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds
1	3/23/31	F	50	14	50	+	69	92	117.0	199	41	92	118.5	179	..	..	.....	...	37	96	128.7
2	4/14/31	M	46	12	47	0	38	118	155.0	129	−5	80	157.0	186	−14	84	153.0	151	6	80	168.5
3	2/11/31	F	62	?	15	?	34	110	96.5	128	41	104	95.5	145	..	..	.....	...	21	98	106.0
4	3/ 2/31	F	63	2	35	0	49	94	130.0	161	..	..	.....	...	..	..	.....	...	38	92	138.0
5	2/ 9/31	M	49	8	25	+	39	90	152.0	...	30	96	152.0	169	..	..	.....	...	14	90	157.7
6	2/14/31	M	44	2	30	+	65	100	138.0	128	57	114	140.0	132	..	..	.....	...	19	98	151.0
7	4/ 7/31	F	32	6	15	0	43	116	122.7	133	17	104	122.5	168	+2	80	120.0	158	−5	82	128.0
8	4/13/31	F	51	168	..	+	61	108	115.5	166	18	94	117.0	181	42	120	116.5	174	31	112	123.7
9	3/19/31	F	31	6	14	0	62	112	78.0	122	57	90	78.0	203	23	106	77.0	213	39	100	87.0
10	3/24/31	F	31	2	35	0	74	118	150.5	85	60	94	150.2	117	41	92	147.0	142	60	124	146.0
11	3/ 7/31	F	36	..	0	?	67	120	141.0	99	39	98	142.5	112	35	98	140.0	136	8	92	146.0
12	3/20/31	F	28	6	9	0	83	132	102.0	95	55	128	102.5	126	..	..	.....	...	58	130	115.0
13	3/ 4/31	F	65	6	40	?	63	106	144.0	...	42	104	144.5	135	35	108	142.0	144	47	118	150.0
14	2/24/31	F	19	6	?	?	74	142	168.0	71	..	...	.....	...	..	...	.....	...	29	110	168.0
15	3/24/31	F	40	6	15	0	56	100	109.7	125	..	...	.....	...	..	...	.....	...	29	79	113.7
16	4/29/31	F	17	6	30	+	61	132	146.0	120	..	...	.....	...	39	118	136.7	115	31	128	154.0
17	5/21/31	F	49	3	20	+	67	100	129.0	96	34	90	129.0	103	25	84	122.5	128	55	96	129.5
18	5/12/31	F	34	14	19	+	104	124	115.7	85	..	...	.....	...	46	76	111.5	96	38	76	124.0
19	4/10/31	M	49	60	15	+	34	98	125.0	162	45	98	127.5	152	..	...	.....	...	4	76	140.0
Total.....			796	325	414		1,143	2,112	2,435.6	2,104	531	1,386	1,176.7	1,952	274	966	1,266.2	1,457	559	1,877	2,574.8
Average.....			42	19	26		60	111	128.2	124	31	99	126.9	151	27	96	126.6	145	29	99	135.5

re and at Varying Periods After Operation

Months After Operation				Six Months After Operation				Nine Months After Operation				One Year After Operation			
Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.
–8	80	114.0	140	–6	76	114.7	132								
–9	56	160.0	140												
+3	66	122.0	157	+5	72	125.7	177								
–2	65	151.0	126	–5	62	112.0	148	–8	72	110.0	139	+2	68	112.0	155
–11	58	110.5	250												
+3	68	121.0	208	+5	72	125.0	177								
–11	79	177.0	179	–2	62	173.7	159	...	..	.....	...	+5	66	176.0	144
–8	60	117.5	186												
–20	68	157.0	111												
+3	69	172.0	131												
–7	80	134.0	144												
–7	68	119.0	227												
–4	80	129.0	158	....	..	.....	...	–11	66	132.0	143				
+4	80	114.0	207	+7	72	117.5	234	–9	72	116.0	228	+9	72	115.0	230
–10	70	129.0	182												
0	80	140.0	195												
–17	68	155.7	147	–6	75	165.0	182	+3	77	168.0	162	+3	72	168.0	162
								–1	78	124.0	186				
–10	70	129.0	156	+18	70	128.0	150	–3	70	128.0	174				
–5	88	117.0	147*	–11	86	113.7	160								
–10	72	128.0	152	–16	68	127.0	120	–4	80	133.0	149	+4	72	131.0	157
+6	106	117.0	216	+5	80	115.0	196								
–5	72	188.0	144	–7	64	192.0	140								
–15	76	147.0	182	–17	68	158.0	173	–4	80	151.0	169	–11	68	157.0	156
–66	1,679	3,148.7	3,885	–30	927	1,767.3	2,148	–37	595	1,062.0	1,370	+12	418	859.0	1,004
–2.9	73	136.9	169	–2.3	71.3	135.9	165.2	–4	66	118.0	171	+2	69	143.1	167

Cholesterol Content of the Blood

After Second Operaiton				Three Months				Six Months				Nine Months				One Year			
Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol Mg. per 100 Cc.
0	84	124.0	148	–10	80	127.7	195	–11	74	127.0	156								
6	88	168.0	151	–33	66	180.0	158	14	58	189.0	180								
8	104	104.0	179	–4	88	116.7	250	..	..	.....	...	....	..	...	...	+20	74	112	186
	...	.....	...	4	62	150.0	208	0	78	168.0	195	....	..	...	...	–4	68	173	207
	...	.....	...	2	90	157.0	143	2	70	175.0	247								
	...	.....	...	–14	60	172.0	169	–9	66	176.0	179								
1	92	116.5	156	–5	68	131.5	152	8	88	132.0	139	+8	88	132	139				
2	120	118.7	174	13	84	132.0	179												
4	94	86.5	161	–10	72	96.0	248												
2	90	141.0	110	11	76	164.0	142	..	..	.....	...	+17	92	179	123				
1	80	143.7	123	–16	62	152.0	171	–14	62	150.0	153								
9	80	111.7	120	21	80	123.0	136	–1	90	124.0	145	....	..	...	...	–14	76	125	132
6	104	147.0	142	9	96	167.0	157												
3	94	162.0	137	–7	86	172.0	181	–10	76	155.0									
20	80	111.0	171	–7	76	121.0	96	–12	76	125.7	134	–12	70	123	118				
	...	.....	...	–9	80	181.0	174	–6	88	187.0	152								
	...	.....	...	2	64	145.0	160												
	...	.....	...	2	68	128.0	134	8	68	124.0	154	....	..	...	...	–7	64	151	178
	...	.....	...	–23	78	151.0	161	–9	70	157.0	157	....	..	...	...	–3	66	148	158
76	1,110	1,534.1	1,772	–74	1,436	2,766.9	3,214	–16	902	1,989.7	1,991	+13	250	434	380	–8	348	709	861
3	93	127.8	148	–4	76	145.6	169	–1	74	153.1	165	+4	83	144	126	–2	69	141	172

following subtotal thyroidectomy performed by one-stage and two-stage operations. The effect on blood cholesterol and that on basal metabolic rate six weeks after hemithyroidectomy are comparable; the percent-

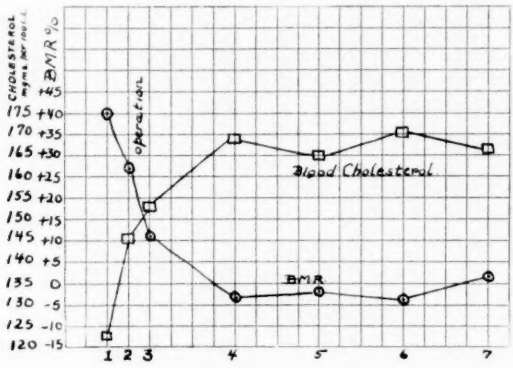

Chart 1.—Effect of preoperative treatment and subtotal thyroidectomy on the basal metabolic rate and blood cholesterol (averages of values found in cases listed in table 1); *1*, on admission to the hospital; *2*, after preoperative treatment; *3*, six days after operation, and *4*, *5*, *6* and *7*, three, six, nine and twelve months, respectively, after operation.

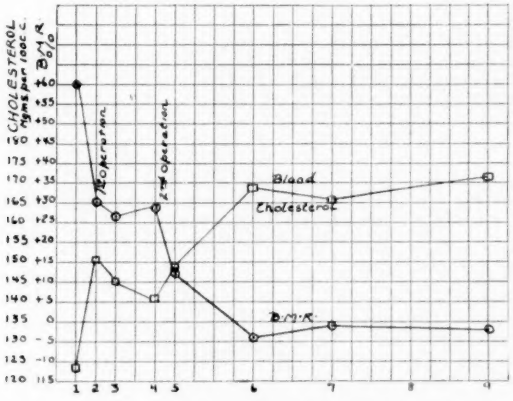

Chart 2.—Effect of subtotal thyroidectomy done in two stages on the basal metabolic rate and blood cholesterol (average values from table 2); *1*, on admission to the hospital; *2*, after preoperative treatment; *3*, six days after hemithyroidectomy; *4*, six weeks later, before second stage operation; *5*, six days after second stage operation, and *6*, *7*, *8* and *9*, three, six, nine and twelve months later, respectively.

age of drop in the basal metabolic rate and the percentage of elevation in cholesterol are approximately half the change in basal metabolic rate

and cholesterol three months following subtotal thyroidectomy done in one stage. This steplike result shows conclusively that more than a hemithyroidectomy is necessary to end hyperthyroidism.

In table 5, the average values for patients followed for three, six and twelve months are given. It was not felt necessary to present the complete data in these cases, as they added nothing to the data in tables 3 and 4. The obtaining of cholesterol values was not complete in these cases following preoperative treatment or immediately after operation, and they were therefore not included in tables 3 and 4.

TABLE 5.—*Exophthalmic Goiter*

A. One-Stage Operation: Results at Three and Six Months

Number of Cases	Before Operation				Three Months After Operation				Six Months After Operation							
	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.
68	42	110	120	126	−4	74	135	162								
21	39	103	123	141	−2	76	137	161	−1	77	133	164				

B. Two-Stage Operation: Results Before First and Second Operation and at Three and Six Months

	Before First Operation				Before Second Operation				Three Months After Second Operation				Six Months After Second Operation			
18	53	107	128	116	29	93	131	149	−2	74	140	177				
13	64	113	128	151	26	94	137	159	−8	72	147	158	−3	76	145	159

C. Results Before Operation and at End of Twelve Months

	Before Operation				At End of Twelve Months			
16	48	104	127	127	+1	70	147	171

Of the cases observed at the end of three months, eight of sixty-eight (not included in tables 3 and 4) showed a lower cholesterol value after operation than before. The greatest drop was from 126 to 53 mg., the drop in the remainder averaging 17 mg. No explanation could be found for these variations. In the group followed for six months, six of the twenty-one showed a lower value three months after operation, while at six months three of these showed values above those noted before operation. At six months nine cases showed lower values than at three months, although they were well above those found before operation. At twelve months, only one patient showed a lower value than that noted before operation.

In chart 3 is shown the smoothed frequency curve in eighty-nine cases before, and three months after, operation. The shift to the right

is obvious, and the "scatter" appears to be greater. This is due chiefly to the fact that higher cholesterol values are found after operation than can rightly be considered normal. A discussion of these higher values will be taken up in the last paper of this study.

In cases in which operation was not followed by persistent hyperthyroidism or myxedema, there appears to be two types of change in the cholesterol values. 1. There is an abrupt rise at the end of three months, occasionally above normal limits, which tends to drop on subsequent observations. In these cases, no evidence of thyroid deficiency appears, as the patient has no complaints. 2. The second type of change is that characterized by a less abrupt increase, followed by increasing values as time goes on and occasionally followed by myx-

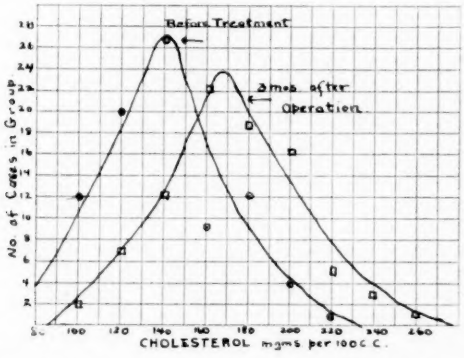

Chart 3.—Smoothed frequency curve of cholesterol value in eighty-nine cases of exophthalmic goiter before treatment and three months after subtotal thyroidectomy. It is to be noted that the "scatter" is greater following operation, and that the peak of the curve has shifted to the right.

edema. Clinical observation reveals that most cases of postoperative myxedema are well established at the end of three months.

Results in Toxic Adenomatous Goiter After Operation.—Thirty-three cases of toxic adenomatous goiter were observed three months after operation. The complete data are included in table 6. Four other cases were checked up twelve months after operation, and the values were all under 200 mg. per hundred cubic centimeters. In only one case of toxic adenomatous goiter seen after operation did hypothyroidism develop. Several cases with rather severe diabetes were encountered. Low cholesterol values were the rule before operation in these cases just as in those without diabetes.

Results in Nontoxic Goiter After Operations.—As a check on the values found in hyperthyroidism, seventeen patients who had had

adenomas or adenomatous goiter were examined from three to twelve months after operation. In these seventeen cases, before operation the average cholesterol value was 198 mg. per hundred cubic centimeters of blood, while after operation the average value was 202 mg. Although a comparison between the values found in persons with toxic

TABLE 6.—*Toxic Adenomatous Goiter: Results in Thirty-Three Cases Before and Three Months After Operation*

			Before Treatment				After Treatment			
No.	Sex	Age	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse	Weight in Pounds	Blood Cholesterol, Mg. per 100 Cc.
1	F	58	40	104	122	122	−15	56	140	172
2	F	53	45	96	154	176	−13	66	164	236
3	M	45	44	96	151	167	+6	60	170	139
4	F	50	48	104	91	120	+2	88	127	186
5	F	49	25	86	113	152	+1	64	119	194
6	F	64	50	104	108	121	−7	72	141	184
7	F	58	14	90	76	124	−5	70	88	180
8	F	50	44	88	138	94	−13	68	156	122
9	F	34	37	150	107	88	−6	68	120	121
10	F	34	41	92	119	138	+18	84	125	146
11	F	58	30	118	155	125	+15	76	151	186
12	F	58	58	96	122	114	−9	68	146	181
13	F	44	40	108	118	156	−5	88	138	214
14	F	58	35	120	119	147	+6	66	135	147
15	F	49	33	88	170	153	+8	84	182	165
16	F	39	35	96	176	198	−6	82	186	187
17	F	44	25	118	118	142	−6	84	132	156
18	F	55	39	98	132	189	0	76	144	238
19	F	48	50	116	147	133	−5	80	165	192
20	M	59	25	80	138	153	−10	59	151	195
21	F	65	33	80	108	99	−12	58	116	162
22	F	56	36	114	143	168	+2	78	130	140
23	F	60	50	98	80	177	−23	80	92	245
24	F	28	40	98	119	92	−5	90	143	167
25	F	64	27	90	110	131	−6	62	108	196
26	F	58	54	112	100	160	+18	84	118	186
27	F	33	30	98	109	176	+2	80	122	180
28	F	35	31	126	124	139	−15	60	129	192
29	F	19	15	104	102	98	−13	90	104	135
30	M	40	24	98	145	205	+17	74	155	213
31	F	65	28	98	112	179	0	62	121	208
32	F	34	19	90	202	188	+7	88	209	212
33	F	56	16	94	92	188	+5	76	100	227
Total.....		1,629	1,161	3,348	4,120	4,812	−67	2,441	4,527	6,002
Average....		49	35	102	122	146	−2	74	137	182

goiter and those found in persons with nontoxic goiter showed an average difference of from 40 to 50 mg., the preceding figures help to confirm the impression that the amount of thyroid secretion is the main factor influencing the level of the cholesterol in thyroid disease.

Recurrent Hyperthyroidism.—Ten of the group of patients with exophthalmic goiter were known to be toxic again on the completion of this study. In these cases, data were obtained which showed a lowering of the blood cholesterol on recurrence or a failure to rise if

hyperthyroidism persisted after operation. In a few cases, in spite of persistent mild toxicity, the value for cholesterol rose in conjunction with a gain in weight and a lowering of the basal metabolic rate.

COMMENT

The results so far set forth indicate a reciprocal relationship, based on average values, between the basal metabolic rate and the blood cholesterol value during fasting. It has been stated [1] that there is no relationship between the level of the blood cholesterol and the basal metabolic rate in people apparently not suffering from thyroid disturbance. This appears to be true at first glance, but it must not be forgotten that the "normal" basal metabolic rate (—10 to +10) is based on averages, and that normal persons may have rates varying 40 points, from minus 20 per cent to plus 20 per cent. The same fact is true for the level of the blood cholesterol. If thyroid extract is administered to a person in whom these two factors can be determined, or the output of the thyroid is diminished by surgical intervention, roentgen treatment or infection, the change in these two variants will tend to be reciprocal. Naturally, other causes which affect cholesterol, such as infection, nephrosis and diabetes, must be excluded.

The effect of preoperative treatment on the blood cholesterol in toxic adenomatous goiter and in exophthlamic goiter was found to be approximately the same. This finding could lead to further discussion as to the effect of iodine in these two clinical types of goiter and as to whether or not there is any fundamental difference between them. As only eight cases were studied preoperatively, a conclusion in this regard would not be trustworthy.

There appears to be a greater variation in the blood cholesterol after operation in exophthalmic goiter than in toxic adenomatous goiter. Assuming that in a case of toxic adenomatous goiter the hyperfunctioning part is confined to the adenomas, removal of these growths should leave a relatively greater portion of normally functioning tissue than in exophthalmic goiter. Surgical treatment of exophthalmic goiter, it seems to me, resembles a tailoring process in which the best results are obtained when the surgeon, through experience in handling the different types of glands in that disease, is able to trim the thyroid to fit individual needs. When he leaves behind a tissue of varying quality and quantity, a good fit, so to speak, is a difficult problem. The size of the remnants left behind in some cases may be several or more times larger than in others. Hence one might expect to find

1. Grabfield, G. P., and Campbell, A. G.: A Note on the Relation Between Blood Cholesterol and Basal Metabolic Rate, New England J. Med. **205**:1148 (Dec. 10) 1931.

patients left with all degrees of thyroid function; in the majority the function is normal or so nearly normal as to escape either the patient's or the physician's attention, and in a few there is still overfunctioning or underfunctioning to an obvious degree.

Is the blood cholesterol of any value in the diagnosis of hyperthyroidism? I think that only general conclusions are warranted in this respect. In part I it was shown that the more severe cases showed the lowest cholesterol levels. If the cholesterol value is below 100 mg. per hundred cubic centimeters in toxic goiter, without acute infection, the patient is almost certainly very toxic. If the cholesterol value is over 180 mg. per hundred cubic centimeters, with or without the previous administration of iodine, there is only slight or moderate toxicity. The determination of the cholesterol content of the blood appears to be of little value in borderline cases, except that if the determination shows a level of over 200 mg. per hundred cubic centimeters, the condition is not likely to be hyperthyroidism unless there has been a complete remission due to the administration of iodine. There are instances of patients with hypertension, goiter, and basal metabolic rates reaching as high as plus 60 or plus 70 in which the clinical evidence is decidedly against hyperthyroidism. In such cases, cholesterol values of 160 or more are usually found, a finding which is out of proportion to the basal metabolic rate, and which serves, I believe, as a definite indication that the thyroid is not the cause of the elevated metabolic rate. On the other hand, I feel that the cholesterol content of the blood is of distinct importance in the diagnosis of hypothyroidism; this will be taken up in part III of this study.

CONCLUSIONS

1. The blood cholesterol is low in toxic thyroid states, and is brought to a normal level partly by preoperative treatment but chiefly by subtotal thyroidectomy.

2. The reciprocal relationship between the average elevation of the basal metabolic rate and the average lowering of the blood cholesterol level in toxic goiter, as was shown in part I of this study, is further confirmed by the results of treatment presented in this paper.

3. There appears to be little difference between the change in the blood cholesterol values in exophthalmic goiter and that in toxic adenomatous goiter as the result of treatment.

4. The blood cholesterol in nontoxic adenoma or adenomatous goiter undergoes little or no change as the result of removal of the growth.

5. The blood cholesterol determination is of distinct but limited value in the diagnosis of hyperthyroidism.

PHYSICAL CHARACTERISTICS OF RESIDUES FROM THE SMALL INTESTINE

HARRY LANDT, M.D.
AND
KATE DAUM, PH.D.
IOWA CITY

The opportunity of observing a patient with an ileostomy led to the following studies on the consistency, color, water and nitrogen content and time of appearance of the material from the small intestine. The reaction of the ileal contents, degree of absorption of the various products of digestion and the exchange of minerals at this level are questions which have been inadequately studied. Reports of work on patients and animals with fistulas, at various points or with varying lengths of the colon excised, have been published from time to time.

The best of the early work is probably that of Heile,[1] who used dogs with ileocecal fistulas. He found that absorption of nitrogen was nearly complete, i. e., 98 per cent on a moderate intake of meat and 88 per cent with great overfeeding. The absorption of carbohydrates fed in the form of rice and sugar was also complete, as was the absorption of milk except when fed in very large amounts. The reaction of the residues was alkaline to litmus; in fact, sufficient alkali was present to neutralize small portions of dilute sulphuric acid. To some extent the alkalinity varied with the diet, being greatest with meat and least with fat. It increased up to the fourth hour after the feeding of meats, but was at its height in the first hour in the case of carbohydrates and fats. On the other hand, Heile found that the absorbing ability of the colon was very small in both man and dogs. Neither the native proteins nor the partially digested proteins, given in the form of enemas, were absorbed, while sugar was utilized to about 20 per cent and water 50 per cent.

Graham and Emery,[2] working on dogs, determined the reaction of the intestinal contents at different levels, particularly after periods of feeding with all meat, all bread and all lard. In these experiments the dogs were killed twenty-four hours after feeding, portions of the intes-

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Nitrogen content and reaction were also studied.

From the Department of Internal Medicine, State University of Iowa.

1. Heile, B.: Experimentelle Beobachtungen über die Resorption im Dunn- und Dickdarm, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **14**:474, 1905.

2. Graham, W. R., and Emery, E. S., Jr.: The Reaction of the Intestinal Contents of Dogs Fed on Different Diets, J. Lab. & Clin. Med. **13**:1097, 1928.

tines tied off, and the reaction of the contents determined colorimetrically. The type of previous feeding had no effect on the reaction, which was slightly acid in the duodenum and jejunum (p_H 6.2 to 6.5), less acid to slightly alkaline in the ileum, and acid again in the cecum. Material from a fistula of the ileum gave a slightly alkaline reaction.

Beuttenmüller,[3] observing a case of ulcerative colitis with a cecal fistula, concluded that the ordinary meal stays in the small intestine two or three hours, a water-poor diet from four to five hours and a fluid diet from one to one and a half hours.

Alvarez and his associates[4] have reported a great deal of work as to the effect of different types of food on the physical properties of the residue collected through the rectum in which an ileorectal anastomosis had been made. They published two series of experiments, a year apart, in which results differed slightly, probably owing to a hypertrophy of the rectum, which was especially marked in one dog. In general, they concluded that the fasting residue was fecal in odor, dark brown in color, of the consistency of thin mush and neutral to litmus. The residue of such foods as liver, gelatin and broth resembled the stools of fasting dogs in color, odor, consistency and reaction. That of carbohydrate foods, such as rice, bread, bananas and sugar, was light canary-yellow and thicker in consistency than the stools of the fasting dogs. The protein foods appeared in four and one-half hours, while the carbohydrates and fats, with the exception of rice and lard, came through more rapidly. The fruits, liquid foods, water and sugar appeared in from fifteen to forty-five minutes. Milk was intermediate, requiring three hours. The percentage relation between the moist weight of the food and the moist weight of the residue was used as an index of digestibility. On this basis, gelatin, sucrose, dextrose, karo corn syrup, meat, rice and cottage cheese showed the smallest percentage of moist residue and therefore the highest efficiency of digestion, whereas fruits, potatoes, bread, raw egg albumin, milk and lactose showed the largest percentage moist residue or the poorest efficiency of digestion. They stressed particularly the fact that raw egg albumin passed through the intestinal tract unchanged and that milk gave consistently very large residues. However, their figures show that small quantities of milk (255 Gm.) have an efficiency of digestion equivalent to rice or cottage cheese. This efficiency of digestion is markedly decreased when the quantity of milk is doubled. The residues had a water content ranging from 83 to 90 per cent. Combinations of certain

3. Beuttenmüller, Helen: Beobachtungen an einer Zoekalfistel, München. med. Wchnschr. **1**:743, 1920.

4. Hosoi, K.; Alvarez, Walter C., and Mann, Frank C.: Intestinal Absorption: A Search for a Low Residue Diet, Arch. Int. Med. **41**:112 (Jan.) 1928.

foods, such as bread and milk and raw egg and milk, improved digestion of both. Lactose proved to be a laxative. Lactose, cheese and lard interfered with digestion the following day. Meat was better digested when fed in lumps than when ground. Foods taken in one large amount were better utilized than when taken in divided portions.

In later work, Alvarez and his co-workers [5] added two dogs with ileal fistulas. In these animals, they found that the taking of food led to the extrusion of material from the fistula with the appearance of the first residues from a given meal in two and one-half hours. Liquids appeared somewhat sooner.

EXPERIMENTAL PROCEDURE

A 19 year old girl, who had had ulcerative colitis of two years' duration and on whom an ileostomy had been done as a therapeutic procedure, was used as the experimental subject. The diagnosis had been established as the result of abundant clinical, roentgen and laboratory evidence, and the patient had fully recovered her health prior to the investigative period.

Collection of material was made in an ileostomy bag which fitted tightly to the opening in the abdomen, the skin being protected by a thick coat of hydrous wool fat. The patient had breakfast at 7 a. m., and the same breakfast was fed on three successive days. Following the breakfasts of the first series, lunch was given at about 12 noon. This was exactly duplicated in a second control series. The third series was similar to the preceding two except that lunch was delayed until all the residue had been excreted from the experimental meal. A fourth series was run in which the breakfast was divided into three feedings an hour apart. Dinner was eaten at 5 p. m. The last of the residue from the dinner meal appeared at the terminal ileum about 5 a. m. Only clear bile-stained fluid was collected at the terminal ileum after this time. The experimental breakfasts were marked off by means of 1 ounce of grapejuice, given at the beginning of lunch. The marking was definite, and proved much more satisfactory than such material as carmine or charcoal. (The daily breakfasts are given in table 1.)

METHODS OF ANALYSIS

The water content of the moist material was determined by weighing the contents of the ileostomy bag and then drying this material to a constant weight. The reaction of the residue was obtained by electrometric titration.[6] Quinhydrone on gold was used in conjunction with a saturated mild mercurous chloride cell. The nitrogen content was ascertained by the Kjeldahl [7] method on 0.5 Gm. of dried pulverized sample. Duplicates were run on all samples.

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5. Childrey, J. H.; Alvarez, W. C., and Mann, F. C.: Digestion Efficiency with Various Foods and Under Various Conditions, Arch. Int. Med. **46**:361 (Sept.) 1930.

6. Clark, W. M.: The Determination of Hydrogen Ions, Baltimore, Williams & Wilkins Company, 1928, chap. 19.

7. Hawk, P. B., and Bergeim, O.: Practical Physiological Chemistry, Philadelphia, P. Blakiston's Son & Co., 1926, p. 711.

RESULTS

Color and Consistency (table 2).—The residues collected by way of the ileofistula varied in color from bright yellow with milk and milk products to a dark green with meat. At no time was a fecal odor noticed. The consistency varied from a curdy, nonhomogeneous, thin

TABLE 1.—*Experimental Breakfasts*

Breakfast	Weight	Dry Weight	Nitrogen
Milk	724	94.2	3.02
	580	75.4	3.05
Bread	90	.....	....
Milk	630	140.0	4.60
Bread	100	.....	....
Water	167	65.0	1.48
Bread	90	.....	....
Water	450	58.5	1.34
Bread	90	.....	....
Butter	60	.....	....
Water	167	111.9	1.45
Bread	90	.....	....
Orange	100	.....	....
Water	167	98.3	1.50
Milk	600	.....	....
Orange	100	91.1	3.5
Meat	175	.....	....
Water	167	62.3	5.2
Cream	600	156.0	2.0
Bread	90	.....	....
Jelly	90	115.6	....
Candy	10	.....	1.04
Water	167	.....	....
Normal breakfast	518	213.0	2.91

TABLE 2.—*Color and Consistency*

Food	Color	Consistency
Milk	Light bright yellow	Curded
Milk and orange	Light bright yellow	Curded, orange particles
Cream	Bright yellow	Curded
Milk and bread	Yellow-green	Thin mush
Bread	Yellow-brown	Smooth, thin mush
Bread and butter	Light yellow-brown	Curded
Bread and orange	Yellow-brown	Semisolid, foamy
Balanced diet	Brown	Curded
Bread, jelly and candy	Dark green	Fluid, smooth
Meat	Black-green	Slightly viscus Smooth thin mush
Milk, divided into 3 feedings	Yellow-green	Very fine curd
Bread and milk, divided feedings	Yellow-green	Smooth, thin mush

gruel-like material with milk, to a smooth, thin gruel with meat. When the food was given at hourly intervals, the consistency was smoother. Feeding of milk at hourly intervals produced a residue of fewer curds and of a less bright yellow color.

Percentage Relation of Dry Residues (table 3).—The percentage relation between the dry weight of the residues and the weight of material ingested varied slightly with the different foods. Some of this

TABLE 3.—*Weight of Residues*

Food	Period I				Period II			Period III		
	Moist Weight, of Food	Moist Weight, Gm.	Dry Weight, Gm.	Per Cent of Food Excreted	Moist Weight, Gm.	Dry Weight, Gm.	Per Cent of Food Excreted	Moist Weight, Gm.	Dry Weight, Gm.	Per Cent of Food Excreted
Milk	724.0	171.5	9.5819	1.3	152.0	6.0682	2.0	191.3	7.4821	2.6
	580.0	149.6	10.7688	1.8	106.2	7.1670	1.8	181.0	9.9329	3.1
Milk	721.3	158.1	10.9868	1.5	.....	.....	...	.....	.....	...
Bread	723.0	193.6	11.7245	1.6	.....	.....	...	.....	.....	...
	690.0	143.6	11.7367	1.7	131.0	7.4299	1.0	220.0	11.0880	1.6
Bread	267.0	99.0	4.5478	1.7	.....	.....	...	.....	.....	...
Water	267.0	154.0	6.7953	2.5	106.5	6.3851	2.3	151.0	6.9042	2.7
	246.0	145.0	6.8579	2.7	.....	.....	...	.....	.....	...
Bread, 450 cc	540.0	146.5	7.3263	1.3	116.4	5.0820	0.9	192.6	8.2500	1.5
Water	520.0	121.7	7.5555	1.4	118.5	5.5347	1.0	203.6	10.1042	1.9
Milk	700.0	200.9	9.2259	1.3	112.0	6.3383	0.9	.....	.....	...
Orange	700.0	181.2	7.5434	1.0	202.6	8.8025	1.2	.....	.....	...
	700.0	198.0	12.0237	1.7	218.5	8.6583	1.2	.....	.....	...
Meat	292.0	101.6	3.3639	1.1	32.0	1.6137	0.5	141.0	4.7760	1.6
	342.0	127.6	5.2161	1.5	141.0	2.6829	0.7	134.0	3.1784	0.9
	342.0	141.9	3.7746	...	.....	.....	...	.....	.....	...
Balanced	498.0	114.2	6.2409	1.2	.....	.....	...	.....	.....	...
	498.0	175.0	7.7527	1.5	.....	.....	...	.....	.....	...
	408.0	165.7	6.2810	1.5	.....	.....	...	.....	.....	...
	408.0	199.8	8.6412	2.1	.....	.....	...	.....	.....	...
Bread	321.0	218.0	5.8528	1.8	121.6	7.2585	2.2	101.4	7.3773	2.2
Jelly	327.0	182.3	6.9122	2.1	186.7	8.1065	2.4	150.0	6.8162	2.0
Candy	.....	.....	.....	...	.....	.....	...	.....	.....	...
Cream	600.0	157.0	6.8931	1.1	111.0	5.1590	0.8	282.0	11.5001	1.9
	415.0	97.9	5.2600	1.2	134.0	6.5415	1.5	183.5	9.1562	2.2

TABLE 4.—*Water Content of Residues*

Food	Weight, Gm.	Period I, per Cent of Water	Period II, per Cent of Water	Period III, per Cent of Water
Milk	724	....	96.1	96.1
Milk	724	94.4	96.1	96.6
Milk	580	92.2	93.9	94.6
Bread and milk	721	93.1	93.5	95.0
	721	93.9	93.7	94.7
	721	....	94.9	....
Bread and water	267	95.4	94.1	95.8
Bread and water	...	95.6	....	95.5
Bread and water	...	95.3	....	95.1
Bread and water	540	95.1	95.7	....
Bread and water	520	93.0	95.4	....
Bread	...	94.4	95.1	....
Butter	317	93.4	94.3	....
Water	...	93.7	96.0	....
Meat	125	96.7	....	....
	175	95.9	95.0	96.7
	175	97.3	97.9	96.1
	175	....	....	95.8
	175	....	....	97.7
	175	....	....	97.6
	...	....	....	95.7
Bread and jelly	321	97.4	94.1	....
Candy	...	96.3	95.7	....
	...	....	93.8	....
Cream	600	95.6	95.4	97.0
	415	94.6	95.2	95.0

Average of all determinations, 94.8%

TABLE 5.—*Time of Appearance of Residues*

Food	Breakfast	First Residue	Marker Appeared	Lunch
Period I				
1. Milk	7:00	9:30	1:40	12:00
Milk	7:00	9:20	2:00	1:10
2. Milk	7:10	9:00		
Bread	7:10	8:25	1:30	12:00
Bread	7:15	8:25	1:30	12:20
Bread	....	....	2:15	12:00
3. Bread				
Water	7:10	10:40	1:30	12:00
Water	7:00	10:15	1:15	12:00
Water	7:00	10:40	1:20	12:00
4. Bread				
Water	7:00	10:00	1:10	12:00
Water	7:00	10:00	12:55	12:00
5. Bread	7:00	8:30	12:55	12:00
Butter	7:00	8:30	1:10	12:00
Water	7:00	9:50	1:00	12:00
6. Bread	7:00	8:30	1:00	12:00
Orange	7:00	8:30	1:00	12:00
	7:00	8:30	1:00	12:00
7. Bread	7:00	8:30	1:30-2:10	1:00-2:00
Butter	7:00	8:30	3:15	2:00
Orange	7:00	8:30	2:45	2:00
8. Milk	7:00	10:30	1:00	12:00
Orange	7:00	9:30	1:10	
	7:00	9:45	1:15	
9. Meat	7:00	11:45	1:00	12:00
	7:00	11:35	1:30	12:00
	7:00	11:15	1:35	12:35
10. Balanced breakfast	7:00	9:00	1:30	12:00
	7:00	9:00	1:25	12:00
	7:00	9:00	1:05	
			1:00	
11. Bread	7:00	9:15	1:10	
Jelly	7:00	8:45	1:00	12:00
Candy				
12. Cream 40%	7:00	8:15	12:50	12:00
	7:00	8:20	1:10	12:00
Period II				
Milk	7:15	8:35	1:45	11:55
Milk	7:10	8:30	1:50	11:55
Milk	7:00	8:55	2:00	11:55
Bread and milk	7:00	8:30	1:15	11:50
Bread and milk	7:00	8:35	1:45	11:55
Bread and milk	7:00	8:35	1:45	11:50
Bread and water	7:00	10:55	1:15	11:50
Bread and water	6:45	9:45	1:10	11:45
Bread and water	6:45	10:15	1:00	11:45
Bread, butter and water	7:00	9:15	12:30	11:45
Bread, butter and water	7:00	9:15	12:35	11:45
Bread, butter and water	7:00	9:00	12:35	11:55
Meat	7:00	11:45	1:00	12:00
Meat	7:00	11:30	12:50	11:55
Cream	7:00	8:30	12:35	11:45
	7:00	8:30	12:35	11:50
Bread	7:00	9:30	1:15	11:50
Candy and jelly	7:00	9:15	1:05	11:50
Candy and jelly	7:00	9:15	1:00	11:55
Period III—Delayed Lunch				
Milk	7:00	9:35	4:45	5:00
Milk	7:00	8:00	4:45	5:10
Milk	7:00	8:30	5:00	5:15
Bread and milk	7:00	8:45	4:45	5:10
Bread and milk	7:00	8:45	4:50	5:00
Bread and water	7:00	9:45	4:45	5:00
Bread and water	7:00	10:00	4:45	5:00
Bread and water	7:00	9:45	5:05	5:15
Meat	7:00	10:30	5:10	5:15
Meat	7:00	10:05	5:05	5:15
Meat	7:00	11:15	5:05	5:15
Meat	7:00	11:15	5:00	5:10
Cream	7:00	8:30	5:10	5:30
Cream	7:00	8:30	5:05	5:15

variation was due, no doubt, to the difference in the amounts of the nonabsorbable constituents of the material fed. This variation was from 1 to 3 per cent and, considering the difference in the amounts and types of food fed, was not remarkable. The weights of the residues obtained in the third period, when the 12 o'clock feeding was omitted, were similar to those in periods I and II.

Water Content of Residues (table 4).—Though the consistency of the different residues varied according to the food fed, the actual water content was found to be remarkably constant. The lowest figure was 92.2 per cent and the highest 97.7 per cent. Most of the residues had a water content of about 94 per cent.

Time of Appearance of Residues (table 5).—The time of appearance of the residue after feeding bore little relation to the amount of the feeding, to the consistency or to the water content. Cream appeared

TABLE 6.—*Reaction of the Residues*

	p_H		p_H		p_H
Milk.....	6.84	Bread and butter.....	7.21	Meat.....	7.78
	7.58		6.88		7.32
			6.89		7.56
Milk and bread.....	7.17				
	7.02	Bread and orange.....	6.55	Balanced breakfast....	7.11
	7.19		6.67		7.08
			7.11		6.58
Bread and water.....	7.16				
	6.41	Milk and orange.....	7.32	Bread, jelly, candy....	6.93
	6.76		6.66		6.46
			6.90		
Bread and water.....	7.23			40% cream.....	7.46

the earliest, 8:15 a. m., and meat the latest, 11:30. The residue of bread and water was extruded after that of bread and milk and bread and butter. The completion time was influenced by the second meal. In general, the breakfast marker appeared from one and one-quarter to one and one-half hours after lunch, whether this was given at 12, 1 or 2 o'clock. In period III, when no meal was given at noon, the marker appeared between 4:45 p. m. and 5 p. m.

Reaction (table 6).—For the most part, the reaction of the residues varied around the neutral point. The lowest or most acid values (p_H 6.4) were with bread, jelly and candy, and with bread and water. The highest or most alkaline reaction was p_H 7.7 with meat.

Nitrogen Content of the Residues (table 7).—Nitrogen was excreted in small amounts, independent for the most part of the amount of nitrogen in the diet. Table 7 shows a variation of 0.09 to 0.45 Gm. nitrogen found in the residues. However, most of the nitrogen weights were from 0.2 to 0.3 Gm. The percentage of nitrogen in the residues varied from 1.6 to 7.8. The highest percentage values were obtained from the meat residues, though the actual amount of nitrogen

excreted following these feedings was no larger than with other foods. Holding the food longer in the body, or giving the food in small frequent feedings did not influence the nitrogen excretion.

Effect of Small Feedings (table 8).—Milk, milk and bread, and meat were given in three feedings instead of one. There was an appre-

TABLE 7.—*Nitrogen Excretion*

Food	Weight, Gm.	Weight of Nitrogen Excreted in Dry Residues, Gm.			Per Cent of Nitrogen in Dry Residues		
		Period I	Period II	Period III	Period I	Period II	Period III
Milk	724	0.3150	0.1435	0.2774	3.2	1.9	3.9
	724	.....	0.1112	0.2602	...	1.8	2.6
	580	0.2487	0.1211	0.4227	2.3	1.6	4.2
Milk and bread	600	0.3390	0.3005	0.2483	3.0	3.3	2.2
	90	0.4168	0.2570	0.4547	3.5	3.3	3.8
		0.3170	0.2302	.....	3.0	3.1	
Bread and water	90	0.1680	0.2509	0.2829	3.6	3.9	2.8
	167	0.2030	.....	0.3164	2.9	...	3.8
		0.2260	.....	0.2551	3.2	...	3.6
Bread and water	90	0.2388	0.1367	.....	3.2	2.9	
	540	0.2274	0.1892	.....	3.0	3.6	
Meat	125	0.1958	0.1258	0.3119	5.8	7.8	6.5
	175	0.3607	0.1016	0.4000	6.9	3.7	7.4
	175	0.2174	.....	0.2449	5.7	...	5.7
	175	.....	.....	0.2015	...	...	6.3
	175	.....	.....	0.2018	...	...	4.2
	175	.....	.....	0.3261	...	...	4.4
Bread, jelly, candy	90	0.2917	0.2410	.....	4.2	3.2	
	60	.....	0.2902	.....	...	3.5	
	10	.....	0.1888	.....	...	3.4	
Cream	600	0.1364	0.0949	0.1948	1.9	1.8	1.6
		0.1421	0.1583	0.2041	2.7	2.4	2.2

TABLE 8.—*Residues from Divided Feedings*

Food	Weight, Gm.	Moist Weight of Residues, Gm.	Dry Weight of Residues, Gm.	Per Cent of Water	Weight of Nitrogen, Gm.	Per Cent of Nitrogen
Milk divided into 3 feedings	724	73.0	4.2715	94.2	0.1750	4.1
	580	115.9	6.4735	94.5	0.2573	4.9
	580	80.4	4.8748	93.9	0.2183	4.4
Milk and bread divided	540	115.3	8.7498	92.5	0.2658	3.0
Meat divided	175	90.8	4.8800	96.1	0.2195	4.3

ciable decrease in the weight of the residues and a change in the consistency and color, but the water and nitrogen contents were unchanged.

SUMMARY

The residues obtained from an ileal fistula varied in consistency and color with the type of food. Milk and milk products gave a curdled yellow mixture; bread and jelly, a dark brown, smooth, thin gruel, and meat, a very dark green, smooth, thin gruel. No fecal odor was noticed at any time. The water content was remarkably constant for all kinds of food (92 to 97 per cent), including a normal breakfast. The nitro-

gen content was approximately constant and was independent of the type or time of feeding. The weight of the residue, either moist or dry, varied with the kinds of food and only slightly with the amount fed. In general, the feeding of milk and milk products resulted in the highest dry residues. The residues appeared from the ileal fistula at one and one-fourth to four and one-half hours after breakfast. Cream appeared from one to one and a half hours after the second feeding. When no second meal was fed, the last of the breakfast residue appeared between 4 p. m. and 5 p. m. Small frequent feedings, particularly of milk, changed the consistency of the residue and the dry and moist weights, but did not affect either the water or the nitrogen contents.

INFLUENCE OF SODIUM NITRITE ON THE CARDIOVASCULAR SYSTEM AND ON RENAL ACTIVITY

IN HEALTH, IN ARTERIAL HYPERTENSION AND IN RENAL DISEASE

SOMA WEISS, M.D.
AND
LAURENCE B. ELLIS, M.D.
BOSTON

The nitrites are chiefly used in the treatment of angina pectoris and related angiospastic disorders; nevertheless they have been and are being widely employed therapeutically for patients with arterial hypertension.

In the present study it was desired to investigate the clinical effects of sodium nitrite on normal persons, on patients with primary arterial hypertension, with or without involvement of the kidneys, and on patients with certain other renal disorders. In addition to observations of the clinical state of the patient, cardiac rate and arterial blood pressure, determinations of the cardiac output were performed; and in particular, investigations were undertaken as to the nature of changes in the renal function as measured by the volume of urine, the urea clearance test of Van Slyke and the creatinine filtrate method of Rehberg. In view of the fact that the nitrites produce vasodilatation and often lower the arterial blood pressure, the effect on renal function through these cardiovascular changes was of particular interest.

MATERIAL AND METHODS

The ten subjects chosen as "normal" were either healthy physicians and medical students or hospital patients convalescent from disorders which had no effect on the cardiovascular system. In all of the twenty-nine patients with arterial hypertension the condition was of the so-called "essential" type, and none had clinical symptoms of renal failure at the time the tests were made. As will be seen, however, the sensitive renal function tests indicated that they suffered to a varying extent from loss of renal reserve. The five cases of glomerular nephritis ranged in severity from mild to very marked. Nine persons in whom unilateral nephrectomy had been performed a year or more prior to this study were also investigated.

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

Six of these were clinically well and had renal functions which were normal or nearly so. The remaining three suffered from complications; two had pyonephrosis, involving the remaining kidney, and one hypertension.

Measurements of blood pressure were performed with a mercury sphygmomanometer, and in some instances were also recorded graphically with a Tycos recording sphygmomanometer. The estimations of the cardiac minute volume outputs were made according to the Fick principle by the method of Field, Bock, Gildea and Lathrop.[1] The technic of Möller, McIntosh and Van Slyke[2] was employed to determine the urea clearance test. In all instances in the accompanying tables the results are expressed as "maximum" clearance, according to the formula,

$$\frac{\text{concentration urine urea}}{\text{concentration blood urea}} \times \text{urine volume per minute}$$

although in certain instances the output of urine fell below 2 cc. per minute, and under such conditions it is known that the urea clearance diminishes. The determination of urea in blood and urine was carried out by the gasometric method.[3] Rehberg's technic for calculating the degree of glomerular filtration by means of creatinine was used,[4] the formula employed being the same as that in calculating the urea clearance, with the substitution of creatinine for urea. The estimation of blood and urine creatinine was performed by the method of Folin,[5] using purified picric acid. For a discussion of the significance of the results obtained in estimating renal function by the urea or creatinine clearance procedure, reference is made to our previous study.[6] In summary, it is believed that both of these procedures are gages of the extent of glomerular filtration and that the creatinine technic probably provides a close absolute index of this filtration. Under conditions of marked diuresis (2 cc. of urine per minute or more) the urea clearance is a relative index of filtration, but when the output of urine falls, increased back diffusion of urea through the tubular walls into the blood serves to lower the urea clearance as compared to the creatinine clearance values.

The creatinine and urea determinations were made on the same specimens of blood and urine, so that the results are comparable. At least 200 cc. of water was given to the subjects each hour during which the tests were carried out in order to provoke a marked diuresis.

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Dosage of Nitrite.—Sodium nitrite in tablet form was administered by mouth. The usual dose administered was from 3 to 5 grains (0.2 to 0.3 Gm.). In the studies on renal function 3 grains of sodium nitrite was administered in water about five minutes before the start of the period of urine collection. Half an hour later another 2 grains (0.13 Gm.) was given, unless the symptoms produced by the first dose were marked in degree. These doses are large therapeutic doses, and in a number of instances produced undesired effects.

EFFECTS OF SODIUM NITRITE

Symptoms.—There was no particular correlation between the symptoms produced and the size of the dose of sodium nitrite. Thus, in one subject 5 grains of sodium nitrite might produce no subjective sensations whatever, while in a second the same amount would cause severe symptoms. Moreover, there was no relationship between the symptoms and the degree of fall in blood pressure except in the cases in which the degree of depression of blood pressure or the intensity of symptoms was marked. The most common subjective sensation complained of was a throbbing headache. Other symptoms were weakness, giddiness and faintness, which in the most extreme cases verged on unconsciousness. Only nine of the fifty-three subjects experienced severe symptoms. Objectively, there was frequently some cyanosis of the extremities, and the peripheral palpable arteries occasionally appeared relaxed under the influence of the nitrite. This dilatation was confirmed by the graphic records, which showed increased amplitude of excursion. When symptoms of faintness, cyanosis, etc., occurred, they usually took place within thirty minutes after the ingestion of the nitrite, although on a few occasions the subject first noticed faintness and giddiness from one to two hours after the administration of the drug, when he rose from the reclining position. Headache occasionally persisted in mild form for several hours.

Heart Rate (tables 1, 2 and 3).—The response of the cardiac rate was not constant. Doses of from 1 to 2 grains (0.06 to 0.13 Gm.) usually produced an insignificant rise or none. With doses of from 3 to 5 grains the average increase in the pulse rate for both normal persons and patients with hypertension was about 8 beats per minute, although in a few instances increases of from 20 to 40 beats were noted. This rise ordinarily lasted less than thirty minutes; in rare instances it persisted for an hour. No relationship was found between the cardiac rate and other symptoms and objective changes.

Arterial Blood Pressure (tables 1, 2 and 3).—The changes in the normal arterial blood pressure which were observed were similar in nature and extent to those noted by others who have studied the effect of sodium nitrite. The action of the drug on the blood pressure was manifest in from five to fifteen minutes after ingestion. The delay

TABLE 1.—*The Effect of from One to Five Grains of Sodium Nitrite on the Heart Rate, Arterial Blood Pressure, Cardiac Output and Basal Metabolic Rate in Normal Subjects and in Patients with Hypertension and with Glomerulonephritis*

Subject	Age, Yrs.	Heart Rate			Arterial Blood Pressure, Systolic/Diastolic, Mm. Hg				Cardiac Output per Minute, L.			Cardiac Output per Stroke, Cc.			Basal Metabolic Rate, per Cent			Dosage, Grains	Symptoms
						Under Sodium Nitrite													
		Before	Under Sodium Nitrite	Difference	Before	Maximum	Average	Difference	Before	Under Sodium Nitrite	Difference	Before	Under Sodium Nitrite	Difference	Before	Under Sodium Nitrite	Difference		
Normal Subjects																			
1	30	72	80	+ 8	113/ 70	83/ 45	100/ 55	−13/−15	6.4	6.9	+0.5	89	86	− 3	+ 3	− 3	− 6	5	Headache
2	36	72	95	+23	113/ 73	96/ 56	100/ 58	−13/−15	6.1	5.8	−0.3	86	61	−25	+12	+37	+25	3	None
3	28	54	60	+ 6	95/ 60	80/ 40	90/ 45	− 5/−15	4.6	4.6	0	85	77	− 8	− 1	− 1	0	3	None
4	28	60	60	0	115/ 68	100/ 50	100/ 58	−15/−10	4.3	4.3	0	72	72	0	+ 2	+ 1	− 1	3	Faintness
5	40	64	70	+ 6	95/ 60	84/ 50	90/ 50	− 5/−10	6.7	6.2	− 0.5	105	88	−17	+ 8	+ 7	− 1	3	None
Subjects with Hypertension																			
6	60	60	84	+24	250/120	172/ 80	195/110	−55/−10	...	...	.....	..	..	....	....	....	....	3	Slight headache
		60	84	+24	270/136	203/120	217/125	−53/−11	...	...	.....	..	..	....	....	....	....	3	Slight palpitation
		60	100	+40	260/120	190/100	210/105	−50/−15	5.6	5.4	− 0.2	93	54	−39	+ 1	+ 2	+ 1	5	Slight headache
		60	85	+25	260/125	197/105	200/110	−60/−15	...	...	.....	..	..	....	....	....	....	5	Slight headache
7	48	72	72	0	235/125	185/100	195/110	−40/−15	3.4	3.1	− 0.3	47	43	− 4	+ 2	− 3	− 5	3	None
8	55	70	70	0	189/100	130/ 75	135/ 75	−54/−25	7.6	5.1	− 2.5	109	73	−36	+11	− 1	−12	3	None
9	55	62	68	+ 6	200/ 95	145/ 70	160/ 80	−40/−15	4.0	3.4	− 0.6	64	50	−14	+ 5	+ 2	− 3	3	None
10	59	72	80	+ 8	220/120	168/ 90	180/100	−40/−20	4.2	4.1	− 0.1	58	51	− 9	+18	+11	− 7	3	Headache
11	55	76	90	+14	207/108	130/ 80	140/ 80	−67/−28	...	...	.....	..	..	....	....	....	....	3	Very faint and pale
12	49	80	95	+15	230/120	165/ 75	175/ 95	−55/−25	...	...	.....	..	..	....	....	....	....	3	None
13	65	76	76	0	210/105	152/100	160/100	−50/— 5	...	...	.....	..	..	....	....	....	....	1	None
14	50	88	88	0	180/110	144/ 95	150/100	−30/−10	...	...	.....	..	..	....	....	....	....	1	None
15	49	94	90	− 4	275/138	232/130	230/132	−43/— 6	...	...	.....	..	..	....	....	....	....	1	None
		88	88	0	236/138	202/122	228/130	— 8/— 8	...	...	.....	..	..	....	....	....	....	2	Slight flush
16	52	80	80	0	224/130	206/126	215/128	— 9/— 2	...	...	.....	..	..	....	....	....	....	1	None
		80	80	0	218/130	194/116	200/120	−18/−10	...	...	.....	..	..	....	....	....	....	2	None
17	24	94	96	+ 2	174/122	158/118	162/120	−12/— 2	...	...	.....	..	..	....	....	....	....	1	None
		96	100	+ 4	174/124	156/116	160/120	−14/— 4	...	...	.....	..	..	....	....	....	....	2	None
18	65	76	80	+ 4	213/120	203/110	210/110	— 3 −10	...	...	.....	..	..	....	....	....	....	3	None
Subjects with Glomerulonephritis																			
19	25	80	90	+10	147/105	130/ 80	130/ 85	−17/−20	...	...	.....	..	..	....	....	....	....	2	Fainted

and variation in the speed with which it acted were probably due to individual differences in the rapidity of absorption from the alimentary canal.

In normal persons when a fall in blood pressure of marked degree occurred, it was occasionally transitory, but usually persisted for about thirty minutes; some lowering of the pressure generally lasted for from one to two hours. In the normal subjects the blood pressure sometimes was not altered, but at times was found decreased by 34 mm. of mercury systolic and 15 mm. diastolic. The average decrease was 12 mm. systolic and 10 mm. diastolic.

In the patients suffering from arterial hypertension the decreased blood pressure tended to persist for a somewhat longer period than in normal persons, and usually lasted about two hours. In a few cases the blood pressure had not entirely regained its former level five hours after the ingestion of the drug, but since the level of the blood pressure in hypertension is notoriously subject to wide fluctuations, it would be unwarranted to ascribe this effect definitely to the nitrite. We have demonstrated [7] that the return of dilated arterioles to a normal state may be independent of the persistence of action of the dilator chemical substance.

The absolute extent of the drop in the pressure in these hypertensive persons was greater than in the control subjects and averaged 35 mm. of mercury systolic and 20 mm. diastolic. However, the percentage decrease was of the same order of magnitude in the two groups. The systolic pressure in the patients with hypertension was almost always reduced to a greater extent than the diastolic. In a few instances extreme lowering of the blood pressure occurred, the pressure in one case dropping from 240 systolic and 130 diastolic to 80 systolic and 70 diastolic. Such dramatic reduction was usually associated with pronounced symptoms, but this by no means invariably occurred. In several cases the pressure fell between 40 and 50 mm. of mercury without the subject experiencing any sensations whatsoever. In two cases the subjects, one normal and the other with chronic nephritis, became faint and cyanotic although the blood pressure changed only from 115 systolic and 68 diastolic to 100 systolic and 50 diastolic and from 147 systolic and 105 diastolic to 130 systolic and 80 diastolic respectively.

Cardiac Output (table 1).—In five normal persons and in an equal number of patients with hypertension, estimations of the cardiac output were performed under basal conditions, both before the administration

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TABLE 2.—*The Effect of from Three to Five Grains of Sodium Nitrite on the Renal Function of Five Normal Persons and Seventeen Patients with Arterial Hypertension*

Subject	Age, Yrs.	Heart Rate			Arterial Blood Pressure, Systolic/Diastolic, Mm. Hg			Blood Urea Nitrogen, Mg. per 100 Cc.		Urea Clearance, Cc.			Creatinine Clearance, Cc.			Urine Volume per Minute, Cc.			Dosage, Grains	Symptoms
		Before	Under Sodium Nitrite	Difference	Before	Under Sodium Nitrite	Difference	Before	Under Sodium Nitrite	Before	Under Sodium Nitrite	Difference	Before	Under Sodium Nitrite	Difference	Before	Under Sodium Nitrite	Difference		
										Normal Subjects										
20	41	68	74	+ 6	104/ 70	104/ 70	0/0	12	13	34 70	68	0	120 129	123	0	0.4 2.2	7.4	+	5	Weak, dizzy
21	42	48	56	+ 8	114/ 70	80/ 60	−34/−10	15	14	61 67	64	0	135 152	130	0	2.4 7.0	6.4	0	5	None
22	22	72	86	+14	104/ 68	100/ 66	− 4/− 2	9	8	70 77	65	0	154 153	121	—	8.9 11.0	3.2	0	5	Headache
23	34	64	72	+ 8	100/ 62	86/ 50	−14/−12	11	..	64 96	72	0	162 180	117	—	1.5 4.3	2.0	0	5	Headache
24	31	61	70	+ 9	102/ 62	90/ 62	−12/ 0	7	7	112 119	86	—	172 136	132	0	4.7 8.0	2.5	0	5	None
										Subjects with Hypertension										
25	70	80	88	+ 8	216/100	164/100	−52/ 0	12	10	69 103	80	0	69 125	105	0	1.6 4.1	4.3	0	3	Cyanotic
26	60	..	..	....	158/102	135/ 85	−23/−17	17	16	58 47	56	0	157 93	127	0	0.8 0.9	1.5	0	5	None
27	39	..	..	....	220/120	170/100	−50/−20	..	..	59 48	45	0	98 86	104	0	10.2 5.8	7.2	0	2	None
28	66	..	..	....	185/ 88	152/ 75	−32/−13	15	14	54 48	47	0	118 112	102	0	4.8 6.3	4.3	0	5	None
29	55	..	..	....	204/120	175/105	−29/−15	27	25	19	20	0	40	37	0	4.8	5.2	0	5	Weak, dizzy; fainted after one hour
30	42	72	80	+ 8	220/138	200/135	−20/− 3	12	12	36 47	51	0	...	...	..	1.4 4.1	5.0	0	5	None
31	61	96	104	+ 8	262/138	225/110	−37/−28	21	20	9 26	21	0	...	...	—	3.0 8.9	4.8	0	5	None
32	25	..	..	....	192/170	175/150	−17/−20	7	..	51 51	47	0	118 110	...	..	4.7 4.3	4.1	0	3	Slight headache
33	46	59	72	+13	144/ 94	132/ 90	−12/− 4	11	9	50	56	0	160	120	—	3.0	3.9	0	5	Headache; cyanosis
34	56	..	..	....	210/ 95	100/ 65	−110/−30	12	13	25 50	23	—	78 82	78	0	0.5 5.2	2.1	0	3	Pale, stuporous
35	45	90	102	+12	154/ 96	152/ 94	− 2/− 2	11	11	54 52	39	—	84 120	99	0	3.3 7.6	6.0	0	5	Slight headache
36	48	..	..	....	210/118	150/100	−60/−18	13	13	53 51	21	—	144 125	122	0	6.0 10.2	2.2	—	5	Slight headache; cyanosis
37	62	..	..	....	190/ 94	160/ 80	−30/−14	13	18	33 61	35	—	107 110	89	—	1.4 8.5	6.6	0	5	None
38	52	67	74	+ 7	210/105	170/ 90	−40/−15	10	9	60	42	—	122	96	—	5.2	4.5	0	5	None
39	65	..	..	....	152/ 80	162/ 62	+10/−18	9	8	51 54	43	—	... 132	96	—	3.2 2.8	3.8	0	5	Headache
40	43	70	72	+ 2	176/ 98	138/ 86	− 38/−12	7	7	54 84 67	31	—	118 142 107	71	—	6.2 9.2 6.5	1.3	—	5	Slight headache; very faint one hour later
27	39	..	..	....	240/130	80/ 70	−160/−60	17	16	59 48	7	—	98 86	7	—	10.2 5.8	0.4	—	5	Pale, cyanotic, stuporous

of sodium nitrite and during the height of its effect. In none of the normal persons was there observed any significant change in the cardiac minute volume output. In all five of the patients with hypertension there was a slight drop in the minute output under the action of the nitrite, but in three of these the decrease was insignificant. In two it amounted to 15 and 32 per cent respectively of the control output. In nine of the ten cases there was a drop in the stroke volume output of the heart, and in six of these it amounted to 15 per cent or more.

Previous studies in regard to the effect of nitrites on the blood flow are rather conflicting. Early work [8] suggested that amyl nitrite and nitroglycerine produced an increase in cardiac output. Lindhard [9] investigated the effect of the inhalation of amyl nitrite in four normal subjects. He found that when they reacted by a slight fall in blood pressure only, the blood flow increased in three and was unchanged in one. When a marked drop in blood pressure resulted, the output was increased in two, unchanged in one and decreased in one. Gaisböck and Jarisch [10] found that the cardiac output increased somewhat in two subjects following the intramuscular injection of from 0.01 to 0.02 Gm. of sodium nitrite, although the pulse rate and blood pressure remained unchanged.

In the present study of the cardiac output, the lowering of the blood pressure in normal subjects was slight or none occurred. The patients with hypertension all showed a significant drop in arterial pressure.

Metabolism (table 1).—In contrast to Meyer [11] who found a decrease in the oxygen consumption in six of seven patients to whom he administered nitroglycerine, we found alteration in the basal metabolism in only one of ten persons given sodium nitrite. In this "normal" person the metabolic rate increased from a level of plus 12 per cent to plus 37 per cent when he was under the influence of sodium nitrite, and was probably due to his apprehensive state.

Renal Function.—The effect of sodium nitrite on renal function was studied thirty-five times in thirty-four subjects. Five of these were normal persons; nine had one kidney only, sixteen suffered from arterial

8. Hewlett, A. W.: The Effect of Amyl Nitrite upon the Blood Pressure in Man, J. M. Research **15**:383, 1906. Cameron, P. D.: Physiological and Pharmacological Studies on Cardiac Tonicity in Mammals, Johns Hopkins Hosp. Rep. **16**: 549, 1911. Hirschfelder, A. D.: Recent Studies upon the Electrocardiogram and upon the Changes in the Volume of the Heart, Interstate M. J. **18**:556, 1911.

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10. Gaisböck, F., and Jarisch, A.: Ueber den Einfluss von Natrium Nitrosum auf den Kreislauf, Wien. klin. Wchnschr. **40**:1540, 1927.

11. Meyer, J.: Contribution à l'étude du mode d'action des nitrites, Arch. d. mal. du cœur **19**:615, 1926.

TABLE 3.—*The Effect of from Three to Five Grains of Sodium Nitrite on the Renal Function of Four Patients with Glomerulonephritis and in Nine Persons with One Kidney*

Subject	Age, Yrs.	Heart Rate			Arterial Blood Pressure, Systolic/Diastolic, Mm. Hg			Blood Urea Nitrogen, Mg. per 100 Cc.		Urea Clearance, Cc.			Creatinine Clearance, Cc.		Urine Volume per Minute, Cc.			Dosage, Grains	Symptoms
		Before	Under Sodium Nitrite	Difference	Before	Under Sodium Nitrite	Difference	Before	Under Sodium Nitrite	Before	Under Sodium Nitrite	Difference	Before	Under Sodium Nitrite	Difference	Before	Under Sodium Nitrite	Difference		
Subjects with Glomerulonephritis																			
41	24	80	88	+ 8	112/ 70	112/ 70	0/ 0	8	7	58 56	60	0	138 137	133	0	8.8 8.5	6.8	0	5	Drowsy
42	47	100	102	+ 2	195/110	168/ 95	−27/−15	119	116	5 5	5	0	2 2	2	0	2.5 3.0	3.0	0	5	None
43	19	..	..	....	140/ 92	120/ 80	−20/−12	11	11	36 52	14	—	95 157	38	—	1.7 5.2	1.0	0	4	None
44	37	80	88	+ 8	146/100	130/ 84	−16/−16	23	22	55 49	25	—	131 116	96	—	3.0 2.8	1.0	—	5	None
Subjects with One Kidney																			
45	43	64	70	+ 6	106/ 70	95/ 62	−11/− 8	12	11	72 70	71	0	76 90	88	0	4.5 7.8	6.8	0	5	None
46	52	70	82	+12	134/ 86	132/ 78	− 2/− 8	15	14	38 33	61	0	56 57	113	0	1.5 1.6	2.6	0	5	None
										116 52	49		104 61	56		9.6 4.7	3.1			
47	23	67	72	+ 5	106/ 70	102/ 72	− 4/+ 2	15	12	75 53	72	0	128 113	97	—	5.0 8.5	4.5	0	5	None
48	27	73	82	+ 9	110/ 76	92/ 64	−18/−12	18	19	55 51	27	—	70 65	53	—	0.7 0.6	0.4	0	3	Fainted
49	44	79	74	− 5	195/120	170/100	−25/−20	18	18	39 32	22	—	66 57	44	—	6.5 7.7	3.7	0	5	None
50	50	85	82	− 3	134/ 84	120/ 70	−14/−14	13	13	95 92	5	—	180 163	13	—	9.3 7.8	0.35	—	5	None
51	42	68	76	+ 8	100/ 64	84/ 66	−16/+ 2	13	10	72 66	60	—	113 105	82	—	9.4 6.8	1.2	—	5	None
52	40	72	75	+ 3	112/ 70	104/ 70	− 8/ 0	5	5	81 75	54	—	142 132	94	—	10.0 5.9	1.3	—	5	None
53	47	70	82	+12	130/ 85	86/ 60	−44/−15	14	15	24 20	5	—	37 34	11	—	2.8 2.5	0.45	—	3	Cyanotic, weak

hypertension and four had glomerulonephritis. The study is summarized in tables 2 and 3. The results obtained in the normal subjects, in those with one kidney and in the patients with hypertension and nephritis were qualitatively similar, and are therefore considered together. It will be seen from a consideration of the data that renal function may be either unchanged or depressed by the action of the nitrite. In no case was there any improvement in renal function. In eleven of the subjects in whom both urea and creatinine clearance tests were performed, and in three in whom urea tests alone were done, there was no evidence of any significant changes in renal activity. In thirteen cases the nitrite caused a reduction in both urea and creatinine clearance. In eight cases there was also a distinct reduction in the total urinary output during the test period, which in six cases reached striking proportions. In eight instances either the creatinine was reduced and the urea was maintained essentially unchanged or the reverse was found. Of the four cases in which this discrepancy was striking, three showed a reduction in the creatinine clearance while the urea clearance was unchanged. The fifth showed the reverse. The interpretation of the findings in these eight cases is difficult. It is conceivable that the nitrite acted on the kidneys so that the usual proportion of back diffusion of urea did not take place in the tubules, and a relatively greater or less amount of urea was excreted than is usual, compared with the total glomerular filtration. It is more probable, however, that the discrepant results were due largely to a summation of the errors inherent in the technical procedures. Once, in case 20, the volume of urine was apparently distinctly increased by the action of the nitrite, but in spite of this there was no evidence of increased glomerular filtration as measured by the urea and creatinine procedures. In twenty-one of the thirty-five cases the nitrite caused a significant lowering of the arterial blood pressure. There was, however, strikingly little correlation between the degree of lowering of the pressure and the decrease in renal function. In those cases in which the drop was extreme, usually accompanied by pronounced symptoms, the urinary output and the excretion of creatinine and urea were ordinarily greatly diminished, but this was by no means invariable. For example, in case 34, in which the nitrite caused the systolic blood pressure to fall 100 mm. and marked cyanosis and a stuporous condition to develop, the urea clearance was only moderately reduced, and the creatinine clearance volume of urine remained unaltered. On the other hand, in several subjects who showed no change in systemic blood pressure, renal function was decreased definitely by the drug.

The subjects investigated had either normal kidneys or all degrees of renal damage, and yet no correlation between the state of the renal

reserve and the effect of the nitrite was observed. Moreover, the patients with hypertension exhibited varying degrees of peripheral arteriosclerosis, and yet no qualitative difference in the action of the nitrite could be ascertained under these circumstances.

COMMENT

The vascular action of sodium nitrite is chiefly, if not entirely, on the peripheral vascular system, and it produces vasodilatation probably as the result of direct action on the smooth muscle of the vessel walls.[12] The site of its activity, therefore, must be chiefly on the arterial side of the vascular bed. There is little or no evidence that in man sodium nitrite produces any direct effect on the capillaries or venules. The fact that the cardiac output is not significantly altered by the drug indicates that if arteriolar relaxation is produced, it is proportionate to the fall of the systemic arterial pressure. The vasomotor center either is unaffected or may be somewhat stimulated as the result of the cerebral ischemia occasioned by the fall in blood pressure.[13]

The action of sodium nitrite differs radically from that of certain other vasodilator substances both pharmacologically and clinically. The symptoms of intense flushing, almost invariably present when histamine or acetylcholine is injected owing to the dilatation of the capillaries and venules of the skin,[14] was absent in all of the fifty-three cases. Moreover, the fact that these two drugs, even in large doses, seldom produce a marked drop in blood pressure suggests either that they cause little or no arteriolar relaxation or that the site of their activity is confined to localized regions of the body; in particular, the splanchnic area may be spared. In contrast to such drugs, sodium nitrite usually produces some, and frequently a very marked, reduction in the arterial blood pressure, which may be unaccompanied by any symptoms whatsoever. The most dramatic symptom which may occur is fainting, and this manifestation was never seen as the result of the administration of histamine or acetylcholine.

In an endeavor to discover whether the depressing effect of the drug on the blood pressure is due either to direct action on the heart or to a diminished cardiac output secondary to decreased venous return, estimations of the minute volume output of the heart were performed. It was found that this did not change materially even in the presence of a

12. Sollmann, T.: A Manual of Pharmacology, ed. 3, Philadelphia, W. B. Saunders Company, 1926, p. 494.

13. Pilcher, J. D., and Sollmann, T.: Studies on the Vasomotor Centre: I. The Effects of the Nitrite Group, J. Pharmacol. & Exper. Therap. **6**:323, 1915.

14. (*a*) Weiss, Soma; Robb, G. P., and Ellis, L. B.: The Systemic Effects of Histamine in Man, With Special Reference to the Responses of the Cardiovascular System, Arch. Int. Med. **49**:360 (March) 1932. (*b*) Ellis and Weiss.[7]

considerable drop in the arterial pressure, although the output per beat was usually somewhat decreased. This state of affairs rules out the possibility that a reduction in the arterial blood pressure is due primarily to a depression of the cardiac minute output.

In a number of instances reduction in the systolic pressure occurred without change in the diastolic pressure or in the blood flow through the heart. A decrease in the systolic blood pressure without change in the output of the heart suggests widening of the lumens of the larger arteries. In view of these changes in the cardiovascular system, the depressor effect on the systolic blood pressure can be explained as due to the following factors, singly or combined: (*a*) a relaxation of the larger arteries and (*b*) a decrease in the stroke volume output of the heart. Thus, the increased volume of the arterial system, resulting from relaxation of the vessel wall, is able to accommodate with a decreased systolic pressure the normal or decreased stroke volume output of the heart. That such a widening of the larger arteries actually occurs is supported by the observation that sodium nitrite causes a relaxation of the temporal and radial arteries and a more bounding pulse, even when there is no change in the stroke volume output of the heart or in the diastolic pressure.

It is well known that in certain types of hypertension, particularly in the malignant form and in eclampsia, the palpable and visible arteries are in a state of constriction. The retinal, temporal, radial, brachial and femoral arteries are examples. We have obtained by means of the roentgen rays, arteriograms of the vessels of the lower extremities during the injection of a solution of potassium iodide into the femoral artery. Comparison with arteriograms taken in normal subjects indicates that the arteries of the leg in certain cases of hypertension are in a state of constriction. It is this difference in the state of the larger arteries that may explain why, after the administration of sodium nitrite, the fall in the systolic blood pressure may be greater in patients with hypertension than in normal subjects.

In contrast to the changes noted in the systolic pressure, a marked drop in the diastolic pressure was seldom observed. Changes in the diastolic pressure are generally indications of alterations in the degree of peripheral arteriolar resistance. This comparative stability of the diastolic pressure suggests that the dilator effect of sodium nitrite on the small arteries and arterioles is not constant or marked. The behavior of those patients who reacted with only a moderate fall in the diastolic pressure and no change in the total blood flow through the heart, but yet showed cyanosis and fainting, suggests that the arteriolar dilatation occurs in different vascular areas to different degrees, with the result that the regional distribution of blood may be very irregular

although the total blood flow remains unaltered. One may assume from the observations in these cases, supported by experimental observations on animals, that a relatively pronounced dilatation of the splanchnic arteriolar system occurs, while the blood flow through the brain is decreased because of a lack of corresponding arteriolar relaxation. This variation in the response of various portions of the arteriolar area is probably due partly to the inherent physiologic characteristics of these vascular areas. However, the variation in the degree and extent of the degenerative vascular changes associated with hypertension in the individual organs is probably the dominating factor which determines the type of response to sodium nitrite in each patient. That the variations in the depressor effect of sodium nitrite are dependent on the state of the vascular system, rather than on a variable action of the drug, is supported also by the parallelism that exists between the effect of sodium nitrite and the depressor effect of stimulation of the carotid sinus in man. As with sodium nitrite, stimulation of the carotid sinus produces slight or no lowering of the blood pressure in normal persons, whereas a pronounced decrease in blood pressure is occasioned in patients with arterial hypertension.[15]

A comparison of the changes which take place in the human vascular system after the administration of histamine,[14a] of acetylcholine [7] or of sodium nitrite demonstrates in an impressive fashion the remarkably adaptable regulatory capacity of the human cardiovascular system. It not only reveals the intimate regulatory connection between the arteries, arterioles, capillaries, venules and veins, but shows that each of these vessels may have an independent function. Each division of the vascular system is capable of changing its caliber independently or in combination with another portion. The relative degree of sensitivity of the same type of vessel in different organs and of different types of vessels in the same organ to various chemical substances makes possible a delicate and economic functioning of the circulation through local or systemic chemical regulation. We have demonstrated how vasodilator chemical substances differ from each other in action and effect. This delicate chemical regulation not only is of significance in the direct regulation of blood vessels, but also has a fundamental association with the indirect reflex control of the circulation.

The literature concerning the effect of nitrite preparations on the function of the kidney presents results that are somewhat in conflict. In 1886 Dana [16] obtained diuresis in five normal persons and six patients

15. Weiss, Soma, and Baker, J. P.: The Carotid Sinus Reflex in Health and Disease: Its Rôle in the Causation of Fainting and Convulsions, Medicine, to be published.

16. Dana, C. L.: M. Rec. **29**:255, 1886.

with renal disease following the administration of nitroglycerine. Loeb [17] felt that this drug had a deleterious effect on renal activity, since he found that in three patients there was a fall in urinary output after its administration. Elliott [18] was of the opinion that "there is no certain correspondence between the amount of urine excreted and the height of the blood pressure. Nitrites as often give an increase as a decrease in the urine output. Studies by Lawrence [19] showed that twelve of sixteen patients with hypertension who received sodium nitrite had an increase in the urinary output and in the phenolsulphonphthalein, total solid and nitrogen excretion. All of these patients also reacted by a lowering of the blood pressure. The reverse results were found by Mason.[20] He performed the Volhard water test on twenty patients, most of whom had hypertension, both under normal conditions and when sodium nitrite was given in 1 grain doses every half hour. In sixteen there was a decrease in water excretion and in four an increase. There was no ascertainable relationship to changes in the systolic or pulse pressure. Cushny [21] stated that "the kidneys are not much affected; occasionally a slight increase in the urine is observed, at other times a decrease, and after large quantities anuria may occur."

The effect of sodium nitrite on the renal activity is entirely due to its vascular action. If the local vasodilatation in the kidneys maintained or increased the glomerular blood pressure and improved renal blood flow, one would expect renal function to increase. Actually in the cases studied by us this never occurred. In one case there appeared to be an increase in urinary output, but the other tests showed no improvement of function. When there is a distinct reduction of the systemic blood pressure it may react unfavorably on the renal blood flow and decrease the renal function. This was by no means an invariable occurrence, however, and in the cases in which the urinary output of solids and water was maintained in the face of a drop in the blood pressure, the local renal vasodilatation must have compensated for the reduction in systemic blood pressure so that the effective filtering pressure remained unaltered.

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17. Loeb, A.: Klinische Untersuchungen über den Einfluss von Kreislaufsänderungen auf die Urinzusammensetzung, Deutsches Arch. f. klin. Med. **84**:579, 1905.

18. Elliott, A. R.: The Treatment of Arterial Hypertension, Am. J. M. Sc. **140**:6, 1910.

19. Lawrence, C. H., Jr.: The Relation of Hypertension to Urinary Excretion, Am. J. M. Sc. **144**:330, 1912.

20. Mason, E. C.: A Note on Water Excretion as Influenced by Blood Pressure Response to Sodium Nitrite, J. Lab. & Clin. Med. **9**:529, 1924.

21. Cushny, A. R.: A Textbook of Pharmacology and Therapeutics, ed. 7, Philadelphia, Lea & Febiger, 1918, p. 392.

In certain cases the renal function was reduced, although the general arterial blood pressure remained essentially unaltered. In these subjects the local vascular changes occurring in the kidneys may have been of such a nature as to decrease the glomerular capillary pressure, and probably consisted in a relatively greater dilatation of the efferent than of the afferent glomerular vessels.

The alterations in renal activity, when they did occur, were largely in the nature of a reduction in glomerular filtration. Changes in tubular activity were less frequent and rarely striking.

Any vasodilating drug which fulfils the criteria demanded in the treatment of arterial hypertension should have a constant, sustained action, should act by dilating the arterioles over all the constricted areas, should not give rise to unpleasant symptoms or side effects and should maintain the normal function of the organs, particularly of the heart and kidneys.[22] These criteria are not fulfilled by the inconstant and transitory action of sodium nitrite. The drug at times produces severe unpleasant symptoms, which are frequently unrelated to the magnitude of the decrease in blood pressure, and may cause depression of renal activity. Although sodium nitrite may have some place in the treatment of vascular crises associated with arterial hypertension, it is of no value in the daily treatment of the condition, and its employment in patients in whom renal insufficiency already exists is irrational.

SUMMARY

1. The study concerns the effect of large therapeutic doses (from 1 to 5 grains) of sodium nitrite by mouth on ten normal persons, twenty-nine patients with primary arterial hypertension, five patients with glomerulonephritis and nine patients on whom unilateral nephrectomy had previously been performed. Qualitatively the effect was the same in each group, but there were certain quantitative differences between the normal subjects and those with hypertension and renal disease.

2. The nitrite inconstantly produced symptoms, an increase in cardiac rate and a depression of blood pressure and renal function. No simple correlation was found between these factors except when they were markedly altered.

3. A decrease of systolic blood pressure was the most frequently observed effect of sodium nitrite. This was caused probably by dilatation of certain parts of the arterial system. The greater the initial degree of arterial tonus, the greater was the drop in systolic pressure. With arterial hypertension this was particularly evident.

22. Weiss, Soma, and Ellis, L. B.: The Rational Treatment of Arterial Hypertension, J. A. M. A. **95**:846 (Sept. 20) 1930.

4. In five normal persons sodium nitrite produced no change in the minute volume output of the heart. In five patients with arterial hypertension this output was doubtfully reduced in three, and reduced 15 and 32 per cent respectively in two. In nine of these ten subjects there was a reduction of the cardiac stroke volume output, which reached 15 per cent or more in six.

5. Sodium nitrite did not affect the basal metabolic rate of nine of ten subjects; it possibly increased the rate in one.

6. The effect of the nitrite on renal function was investigated thirty-five times by simultaneous determinations of the urinary output and urea and creatinine clearance tests. In no case was the renal activity improved. In fourteen instances there was no change in renal function; thirteen times it was definitely decreased, and on eight occasions it was questionably lowered.

7. Physiologic changes which occur in the human cardiovascular system as a result of the action of sodium nitrite are discussed and correlated.

8. The use of sodium nitrite in the routine treatment of arterial hypertension with the hope of maintaining the blood pressure at a relatively low level is illogical and may be dangerous.

Miss Rose Shore and Miss Mary D. Baker furnished technical aid in this investigation.

A COMPARATIVE STUDY OF BLOOD CULTURES TAKEN WITH KENDALL AND ROUTINE MEDIUMS

CHARLES K. FRIEDBERG, M.D.
NEW YORK

The failure or difficulty of cultivating artificially the etiologic agents in a number of so-called virus diseases which are contagious and probably infectious, such as smallpox, influenza, poliomyelitis and others, has often been ascribed to improper mediums. Recently Kendall [1] expressed the belief that the difficulty in cultivating viruses was due to a departure of the mediums commonly employed from the environment of the organisms in nature. He pointed out that the artificial mediums usually employed contain protein degradation products (peptones and meat extracts) and little or no unaltered protein, whereas the body tissue possesses the unaltered protein without its hydrolytic products. In order to provide an artificial environment more nearly simulating the natural one in this respect, he prepared a medium (K medium) containing the unaltered protein without peptones or other substances resulting from its disintegration.

With this medium Kendall claimed to have isolated from the blood of three patients with influenza a coccus which existed in the blood in a filtrable state, but which by repeated transplants in K medium and subcultures on agar could be transformed into a visible, nonfiltrable organism. In the filtrable form it grew on K medium, but did not grow visibly in peptone medium. Injection of the coccus in the filtrable state into the rabbit induced an infection simulating influenza, but inoculations with the nonfiltrable (coccus) form were unsuccessful. Furthermore, Kendall claimed to have converted a number of other organisms into filtrable forms and to have recovered them, following filtration, in their ordinary nonfiltrable state. Among these were Bacillus typhosus, Bacillus paratyphosus A, Staphylococcus aureus, Noguchi's Leptospira icteroides, Dochez's scarlet fever streptococcus and Rosenow's poliomyelitis streptococcus. He also stated that staphylococcus phage filtrates and Besredka's staphylococcus antivirus had yielded typical cultures of Staph. aureus. Furthermore, Kendall stated that he had obtained positive growth in blood cultures quite readily in a series of cases of

From the Department of Laboratories of the Mount Sinai Hospital.

1. Kendall, A. I.: Science **74**:129 (Aug. 7) 1931.

common cold, arthritis, rheumatic fever, rheumatoid endocarditis, measles (thirty hours before the rash) and German measles, while cultures on ordinary artificial mediums in the same cases gave no growth.

In the work to be reported I have made a comparative study of the results of blood cultures made according to Kendall's method employing the K medium and of results of simultaneous blood cultures made according to the routine method with the ordinary artificial mediums employed in the laboratories of the Mount Sinai Hospital.

METHOD

The routine method was performed as follows: The equipment, consisting of a sterile syringe and needle, three Petri dishes and mediums, was arranged on a sterile towel at the bedside. Fluid and solid mediums were used. There were three flasks of the former, each of 100 cc. capacity, containing about 75 cc., respectively, of plain broth, dextrose broth (2 per cent dextrose) and tomato-dextrose-peptone broth. Solid mediums were prepared by pouring three plates from tubes containing 10 cc. of plain agar, dextrose agar and liver hormone agar, respectively, with similar amounts of plain broth in tubes. While the equipment was being arranged, the tubes of agar were liquefied by being heated in boiling water. These were then cooled to from 45 to 50 F. in ice water provided at the bedside. From an arm vein, 21 cc. of blood was taken aseptically, and 2 cc. was added to each of the tubes of liquefied agar, dextrose agar and liver hormone agar. These were poured back and forth into the tubes of broth and then into the Petri dishes, where the mediums were permitted to harden. Five cubic centimeters of blood was inoculated into each of the three flasks. The flasks and plates were then incubated at 37 C. Subcultures from the flasks were made on the following day and repeated daily thereafter for several days (if no growth occurred) into 1 per cent dextrose broth and ascitic fluid plus 1 per cent dextrose agar slants. Plates and flasks were examined daily for four days.

During the course of this work the routine method was modified by substituting in place of the flask of tomato broth a 100 cc. flask containing 75 cc. of K medium prepared according to the method described by Kendall.[1] Fresh hog's intestine was opened, cleaned, ground in a meat chopper and immersed in four times its volume of a 95 per cent solution of alcohol. Extraction was carried out at 37 C. for two days with occasional stirring. The alcohol was then removed and extraction repeated with fresh alcohol (altogether three extractions). The dry tissue was then subjected to reextraction with benzene to remove the remaining lipoidal constituents. The benzene was removed by filtration, air current and exposure to the air for several days. The material that remained after extraction of the lipoidal elements was then reground to a fine powder. The powder when ready for use was added to Tyrode's solution (2 per cent by weight of dry intestine was used). The suspension was autoclaved and adjusted to a p_H of from 7 to 7.4 by means of sodium bicarbonate. Seventy-five cubic centimeters of the medium was used for each blood culture; it was placed in an Erlenmeyer flask of 100 cc. capacity, and this replaced the flask containing tomato medium in the routine method. For routine purposes, any given blood culture was performed as already described, using however only the two remaining routine flasks and the three routine plates. Somewhat more than the usual 21 cc. of blood was drawn, after 16 cc. of it (2 cc. in each of the three solid mediums

and 5 cc. in each of the two flasks) was inoculated into the routine mediums; the remaining 5 to 10 cc. was inoculated into the Kendall flask at the bedside. The routine flasks and plates were studied and subcultured as already described. The Kendall flask was simultaneously incubated at 37 C. Smears from the Kendall flask were made daily; if a smear was positive, or if clouding occurred, subcultures were made from this flask into one tube containing 10 cc. of K medium, one tube of 1 per cent dextrose broth and one tube of ascitic fluid plus 1 per cent dextrose agar. If the primary culture on K medium was negative, incubation was continued for ten days; then a transplant was made to another tube of K medium. After three such transplants at intervals of ten days, the medium of the final transplant was filtered through a Berkefeld N candle and streaked onto plates of peptone agar containing about 25 per cent K medium.[2] These plates were incubated at 37 C. anaerobically for three days and aerobically for four days and then examined for growth.

CLINICAL MATERIAL

Special cases were not chosen for this study; blood cultures were performed as a routine when they were requested by the medical, surgical and special divisions of the hospital. While the indications for these blood cultures differed somewhat in the various hospital services, the cultures were generally requested for patients of the following descriptions:

Patients with the clinical features of a general infection (bacteremia), particularly when some local infection served as an obvious portal of entry
Patients with an obvious local infection who, after operation, presented symptoms of a general infection
Patients with the clinical features of typhoid fever or subacute bacterial endocarditis
Patients with rheumatic cardiovalvular diseases with fever.
Patients with otitic symptoms including fever, especially when thrombosis of a sinus or of the bulb of the jugular vein was suspected.
Patients with fever of uncertain etiology
Patients with lobar pneumonia and meningococcic meningitis
Patients with terminal cystitis and ascending pyelonephritis

One hundred and three blood cultures were taken from seventy-seven patients. The clinical diagnoses on these patients may be classified as in table 1.

Most numerous were those cases (15, with twenty-three blood cultures) in which the presence of a local infection which might serve as an obvious portal of entry, combined with a protracted febrile course, suggested the possibility of a bacterial invasion of the blood stream. Under "local infection" are included cases of gonorrheal arthritis and salpingitis, suppurative adenitis, osteomyelitis and other suppurative

2. Tubes of plain agar were melted in boiling water, mixed with 25 per cent by volume of K medium, poured into a Petri dish and permitted to harden. Except when otherwise indicated, all agar mediums contained peptone.

processes. The cases designated under "postoperative fever" were likewise associated with an infected focus and with continued fever, developing after operation or other surgical trauma, which suggested that a bacteremia had been precipitated. Another large group was formed by cases of acute otitis media or mastoiditis in which blood cultures were made to determine the presence of sinus thrombosis. In cases which presented a picture highly suggestive of, or definitely that of, subacute bacterial endocarditis, blood cultures were taken as a routine to confirm the diagnosis. There were, in addition, six cases of chronic cardiovalvular disease with fever, three of which presented the clinical features of acute articular rheumatism. Blood cultures were made in these cases because of the possibility of bacterial endocarditis without

TABLE 1.—*Summary of Clinical Material*

Diagnosis	Number of Cultures	Number of Patients
Local infection, including gonorrhea, arthritis and salpingitis	23	15
Postoperative fever	10	8
Otitic infection	13	11
Subacute bacterial endocarditis	9	6
Chronic cardiovalvular disease with fever, including rheumatic fever	8	6
Genito-urinary infection	8	6
Pulmonary infection:		
Lobar pneumonia	9	7
Bronchopneumonia and upper respiratory infection	4	4
Tuberculosis	2	2
Contagious diseases	7	5
Meningitis:		
Meningococcus	4	4
Pneumococcus	2	1
Metastatic carcinoma	4	2

the complete clinical manifestations. Eight blood cultures were made in six cases of genito-urinary infections in which, particularly in the terminal stages, bacterial invasion of the blood stream was apt to occur. Nine blood cultures were made in seven cases of lobar pneumonia. There were four cases of meningococcic meningitis in which blood cultures were taken early in the course of the disease. The remaining blood cultures were made in cases of bronchial pneumonia and infections of the upper respiratory tract, tuberculosis, contagious diseases, and metastatic carcinoma, generally on admission, when the differentiation from a general infection of the blood was not clear.

BACTERIOLOGIC RESULTS

Table 2 shows the comparative results obtained with the K medium and with routine culture mediums, the tomato flask being omitted.

In nineteen cultures, both methods gave positive growth, and both gave identical organisms. It is well to point out that in these instances

TABLE 2.—*Comparative Results of Blood Cultures Made with K Medium and by the Routine Technic*

Blood Culture		Diagnosis	Growth Obtained by	
			Routine Method	Kendall's Method
95	2	Pneumococcic meningitis	Staph. albus	Staph. albus
98	4	Lobar pneumonia	Pneumococcus, type III, in plain broth and on all plates	Pneumococcus, type III
110	7	Osteomyelitis of fourth lumbar vertebra	Staph. aureus in dextrose flask; no growth in other flasks or on plates	No growth
115	12	Subacute bacterial endocarditis	Str. viridans (*a*)	Str. viridans (*a*)
122	15	Lobar pneumonia	Pneumococcus, type I, in all except plain agar	Pneumococcus, type I
130	19	Lobar pneumonia	Pneumococcus, type IV, in all except plain agar	Pneumococcus, type IV
139	27	Meningococcic meningitis	Meningococcus	Meningococcus
141	28	Acute sinusitis; encephalomyelitis	Str. haemolyticus (*β*) in flasks; no growth on plates	Str. haemolyticus (*β*)
142	29	Carcinoma of prostate with metastasis to bones	B. coli	B. coli
143	30	Furuncle of neck	Staph. albus	Staph. albus
150	35	Subacute bacterial endocarditis	Str. viridans (*a*)	Str. viridans (*a*)
165	47	Meningococcic meningitis	Meningococcus	Meningococcus
168	49	Suppurative inguinal adenitis	Staph. albus	No growth
172	51	Lobar pneumonia	Pneumococcus, type II, dextrose broth; no growth in plain broth	Pneumococcus, type II
174	53	Thrombosed prolapsed hemorrhoids, postoperative	Gram + cocci only anaerobically	No growth
188	64	Carcinoma of prostate with metastasis to bones	B. coli (no growth in plain flask)	B. coli
192	68	Epididymo-orchitis; postoperative peritonitis	Str. haemolyticus (*β*)	Str. haemolyticus (*β*)
199	71	Subacute bacterial endocarditis	Str. viridans (*a*)	Str. viridans (*a*)
215	82	Arsphenamine dermatitis	Staph. aureus in two flasks; no growth on plates	Staph. aureus
223	89	Subacute bacterial endocarditis	Enterococcus	Enterococcus
225	91	Carcinoma of prostate with metastasis to bones	B. coli	B. coli
233	98	Abscess of brain ?	Str. haemolyticus (*β*)	Str. haemolyticus (*β*)
240	103	Subacute bacterial endocarditis	Enterococcus	Enterococcus
94	1	Pyelonephrosis	No growth	No growth
97	3	Bilateral acute mastoiditis	No growth	No growth
104	5	Postoperative bronchopneumonia	No growth	No growth
108	6	Meningococcic meningitis	No growth	No growth
111	8	Lobar pneumonia; phlebitis	No growth	No growth
112	9	Pneumococcic meningitis	No growth	No growth
113	10	Chronic cardiovalvular disease; bronchopneumonia	No growth	No growth
114	11	Lobar pneumonia	No growth	No growth
116	13	Meningococcic meningitis	No growth	No growth
121	14	Malaria	No growth	No growth
123	16	Perinephritic abscess	No growth	No growth
128	17	Suppurative adenitis	No growth	No growth
129	18	Cholelithiasis and cholecystitis (postoperative)	No growth	No growth
131	20	Osteomyelitis of fourth lumbar vertebra	No growth	Gram-positive cocci which did not grow out
132	21	Hydrosalpinx; postoperative pneumonia	No growth	No growth
133	22	Chronic cardiovalvular disease	No growth	No growth
134	23	Lobar pneumonia	No growth	No growth
136	24	Acute mastoiditis	No growth	No growth

TABLE 2.—*Comparative Results of Blood Cultures Made with K Medium and by the Routine Technic—Continued*

Blood Culture		Diagnosis	Growth Obtained by	
			Routine Method	Kendall's Method
137	25	Subacute bacterial endocarditis	No growth	No growth
138	26	Inguinal hernia, postoperative	No growth	No growth
145	31	Mastoiditis	No growth	No growth
146	32	Acute otitis media	No growth	No growth
147	33	Acute otitis media	No growth	No growth
149	34	Lobar pneumonia	No growth	No growth
152	36	Suppuration of the neck	No growth	No growth
153	37	Upper respiratory infection; posttonsillectomy fever	No growth	No growth
154	38	Amputation of leg	No growth	No growth
155	39	Rheumatic fever	No growth	No growth
156	40	Mastoiditis	No growth	No growth
157	41	Lobar pneumonia	No growth	No growth
158	42	Incomplete abortion	No growth	No growth
159	43	Furuncle of neck	No growth	No growth
161	44	Abscess of finger; lymphangitis	No growth	No growth
163	45	Acute otitis media	No growth	No growth
164	46	Rheumatic fever	No growth	No growth
167	48	Subacute bacterial endocarditis	No growth	No growth
171	50	Infected thrombosed hemorrhoids; postoperative fever	No growth	No growth
173	52	Osteomyelitis of fourth lumbar vertebra	No growth	No growth
175	54	Rheumatic fever	No growth	No growth
177	55	Typhus	No growth	No growth
178	56	Epididymo-orchitis; postoperative peritonitis	No growth	No growth
179	57	Gangrenous ulceration of skin of neck	No growth	No growth
180	58	Gonorrheal salpingitis	No growth	No growth
182	59	Upper respiratory infection; bronchopneumonia	No growth	No growth
183	60	Subacute bacterial endocarditis	No growth	No growth
184	61	Acute mastoiditis; erysipelas	No growth	No growth
186	62	Acute mastoiditis; erysipelas	No growth	No growth
187	63	Acute otitis media	No growth	No growth
189	65	Typhus fever	No growth	No growth
190	66	Disseminated bronchopneumonia	No growth	No growth
191	67	Acute mastoiditis	No growth	No growth
194	69	Typhus fever	No growth	No growth
195	70	Chronic cardiovalvular disease	No growth	No growth
200	72	Primary thrombosis of bulb of jugular vein	No growth	No growth
201	73	Rheumatic fever; chronic cardiovalvular disease	No growth	No growth
202	74	Chronic glomerulonephritis, exacerbated	No growth	No growth
203	75	Bronchopneumonia	No growth	No growth
204	76	Ascending pyelonephritis	No growth	No growth
206	77	Bronchopneumonia	No growth	No growth
208	78	Cystectomy for carcinoma of bladder; postoperative fever	No growth	No growth
210	79	Abscess of brain	No growth	No growth
211	80	Carcinoma of cecum with metastasis	No growth	No growth
214	81	Empyema; phlegmon of thoracic wall	No growth	No growth
217	83	Bronchopneumonia	No growth	No growth
218	84	Ulcerative colitis	No growth	No growth
219	85	Diabetes; otitis media	No growth	No growth
220	86	Ascending pyelonephritis	No growth	No growth
221	87	Erysipelas; carcinoma of pancreas	No growth	No growth
222	88	Infectious mononucleosis	No growth	No growth

TABLE 2.—*Comparative Results of Blood Cultures Made with K Medium and by the Routine Technic—Continued*

Blood Culture		Diagnosis	Growth Obtained by: Routine Method	Growth Obtained by: Kendall's Method
224	89	Scarlet fever	No growth	No growth
226	92	Brill's disease	No growth	No growth
227	93	Ascending pyelonephritis	No growth	No growth
229	94	Rheumatic fever	No growth	No growth
230	95	Disseminated miliary tuberculosis	No growth	No growth
231	96	Subacute bacterial endocarditis	No growth	No growth
232	97	Ascending pyelonephritis	No growth	No growth
234	99	Acute glomerulonephritis	No growth	No growth
235	100	Suppuration of neck	No growth	No growth
236	101	Chronic glomerulonephritis	No growth	No growth
237	102	Lobar pneumonia	No growth	No growth

the results with the routine method were based on the findings in two flasks and three plates containing 16 cc. of blood. Thus in any given positive result one or more of these five units may have shown no growth. On the other hand, the positive growths obtained with the K medium were found in single flasks each of which had been inoculated with from 5 to 10 cc. of blood. Thus, in culture 4, the routine medium as well as the K medium showed Pneumococcus, type III, but the plain broth flask was negative. Similarly in blood culture 51 Pneumococcus, type II, did not grow in the plain broth flask. Similar instances in which positive growths by the routine method were obtained in less than the entire five units follow: In culture 64, the plain flask was negative for Bacillus coli; in cultures 15 and 19, Pneumococcus did not grow on the plain agar plates; in culture 82, Staph. aureus did not grow on any of the plates.

On the other hand, there were four cultures in which positive results were obtained by the routine method and negative results by use of the K medium. In culture 7, representing a case that clinically appeared to be one of osteomyelitis of the fourth lumbar vertebra running a septic course, Staph. aureus grew out in the dextrose flask, but not in the other flask or on the plates. The Kendall flask was likewise negative. It is well to note that in a later culture made from the same patient's blood (culture 20) the result was negative by both the routine and the Kendall method. In culture 30, representing a case of furunculosis of the neck, the routine method produced one colony of Staph. albus per cubic centimeter; the Kendall flask was negative. In culture 53, the routine aerobic mediums as well as the Kendall medium, showed no growth, but the anaerobic medium yielded gram-plus cocci. This culture was from a patient who had been operated on for thrombosed, infected hemorrhoids. An earlier aerobic culture of this patient's blood (culture 50) was negative on both the routine mediums and the Kendall

medium. Finally, routine culture of the blood of a patient with suppurative inguinal adenitis and a septic temperature curve showed two colonies of Staph. albus per cubic centimeter, while culture of the blood on the K medium showed no growth. I observed, therefore, that cultures on the K medium showed no growth in those instances in which the cultures by the routine method indicated an invasion of the blood stream with few organisms, or in which by the routine method only individual plates or flasks showed positive growth, or in which growth was obtained only by anaerobic culture. The remaining seventy cultures both on the routine mediums and on the K medium gave negative results. Further study was conducted to determine whether or not in a number of cases filtrable forms of an organism were present which might be transformed to the ordinary nonfiltrable state, and also to determine whether or not it was possible to convert the common organisms obtained in the positive cultures into filtrable forms and then recover them in a nonfiltrable state as claimed by Kendall.

When a culture on K medium was positive, it was subcultured in a tube containing 10 cc. of K medium. This was incubated ten days. Subculture was then repeated at intervals of ten days until three subcultures had been obtained. Smears were made at this point from the final subculture; if a smear was positive, the organism was isolated. The final subculture was then filtered rapidly through a small Berkefeld N filter. The filtrate was streaked onto plates containing agar with about 25 per cent of K medium. Smears were made of the filtrate; if a smear was positive, the organism was isolated. The plates were then incubated for three days at 37 C. in anaerobic jars [3] and then aerobically for four days.

When a culture on K medium was negative, the original flask was incubated ten days before subcultures were made, and the identical procedure used with the positive culture was followed. Table 3 shows the results obtained.

Of nineteen positive cultures, eleven were preserved through three subcultures. Before filtration the organisms were clearly visible on smear and could be isolated on ordinary mediums or on K medium. After the third subculture from each positive growth had been passed through a Berkefeld N candle, the organisms were present in four of the filtrates and on incubation anaerobically and aerobically grew out on the hog's intestine-agar plates.[4]

Two of these were enterococci,[5] one was Bacillus coli, and one was Staph. aureus. The other seven cultures in repeated subcultures of

3. Cohen, J.: J. Lab. & Clin. Med. **15**:262 (Dec.) 1929.

4. These plates contained plain agar with 25 per cent of Kendall's hog's intestine medium, as described under "Methods."

5. These were gram-positive, nonhemolytic cocci, growing in chains and "diplo" forms, which fermented esculin.

which the organisms remained visible, gave no visible organisms on filtration, nor any growth on transfer to and incubation of the agar plates. Similarly the eight positive cultures in which the organisms could not be preserved on subcultures, gave no growth after filtration or on transfer to the agar plates. Thus the ordinary organisms, when

TABLE 3.—*Summary of Results with Cultures on K Medium*

Blood Culture		Original K Culture	Before Filtration After 3 Subcultures	After Filtration	After 7 Days' Incubation
95	2	Staph. albus	No growth	No growth	No growth
98	4	Pneumococcus, type III	No growth	No growth	No growth
115	12	Str. viridans	No growth	No growth	No growth
122	15	Pneumococcus, type I	Pneumococcus, type I	No growth	No growth
130	19	Pneumococcus, type IV	No growth	No growth	No growth
139	17	Meningococcus	No growth	No growth	No growth
141	28	Str. haemolyticus (β)	No growth	No growth	No growth
142	29	B. coli	B. coli	No growth	No growth
143	30	Staph. albus	No growth	No growth	No growth
150	35	Str. viridans	Str. viridans	No growth	No growth
165	47	Meningococcus	No growth	No growth	No growth
172	51	Pneumococcus, type II	No growth	No growth	No growth
188	64	B. coli	B. coli	B. coli	B. coli
192	68	Str. haemolyticus (β)	Str. haemolyticus (β)	No growth	No growth
199	71	Str. viridans	Str. viridans	No growth	No growth
215	82	Staph. aureus	Staph. aureus	Staph. aureus	Staph. aureus
223	89	Enterococci	Enterococci	Enterococci	Enterococci
225	91	B. coli	B. coli	No growth	No growth
233	98	Str. haemolyticus (β)	Str. haemolyticus (β)	No growth	No growth
240	103	Enterococcus	Enterococcus	Enterococcus	Enterococcus
94	1	No growth	No growth	No growth	No growth
97	3	No growth	Diphtheroids (contaminant)	No growth	No growth
104	5	No growth	No growth	No growth	No growth
108	6	No growth	No growth	No growth	No growth
110	7	No growth	No growth	No growth	No growth
111	8	No growth	No growth	No growth	No growth
112	9	No growth	No growth	No growth	No growth
113	10	No growth	No growth	No growth	No growth
114	11	No growth	B. subtilis (contaminant)	No growth	No growth
116	13	No growth	B. subtilis (contaminant)	No growth	No growth
121	14	No growth	No growth	No growth	No growth
123	16	No growth	No growth	No growth	No growth
128	17	No growth	Diphtheroids	Diphtheroids	Diphtheroids
129	18	No growth	No growth	No growth	No growth
131	20	No growth	No growth	No growth	No growth
132	21	No growth	No growth	No growth	No growth
133	22	No growth	No growth	No growth	No growth
134	23	No growth	No growth	No growth	No growth
136	24	No growth	B. subtilis	B. subtilis	B. subtilis
137	25	No growth	Diphtheroids	Diphtheroids	Diphtheroids
138	26	No growth	No growth	No growth	No growth
145	31	No growth	No growth	No growth	No growth
146	32	No growth	No growth	No growth	No growth
147	33	No growth	No growth	No growth	No growth
149	34	No growth	No growth	No growth	No growth
152	36	No growth	No growth	No growth	No growth
153	37	No growth	No growth	No growth	No growth
38-45		No growth	No growth	No growth	No growth
164	46	No growth	Diphtheroids (contaminant)	No growth	No growth
48-50		No growth	No growth	No growth	No growth

obtained from blood cultures, could not be converted into filtrable forms, and transfer to ordinary mediums did not restore the usual nonfiltrable state.

Of the eighty-three cultures that in the original Kendall flasks were negative, nine were contaminated after being subcultured three times, six by diphtheroids and three by Bacillus subtilis. In four cultures, the contaminants passed through the Berkefeld filters (in three, diphtheroids; in one, B. subtilis) and were grown in pure culture on

the hog's intestine-agar plates after seven days' incubation, as previously described. The seventy-four cultures that remained persistently negative on subculture in the Kendall tubes gave no growth in any case on being transplanted to ordinary peptone medium. That is, in no instance in which a routine blood culture failed to show growth was a positive result obtained in the original Kendall flask or on repeated subculture, filtration and incubation on ordinary mediums, so that there was no possibility of invisible, filtrable forms of organisms being present in the blood of any of these patients.

COMMENT

In this study I have considered the K medium from two points of view; first, that of its employment in routine blood cultures and, second, that of its alleged capacity for isolating filtrable forms of various organisms. In regard to the first, I have observed the results obtained by the use of K medium in comparison with those obtained by the routine procedure practiced in the laboratories of the Mount Sinai Hospital. In one hundred and three cultures there were four discordant results; i. e., the K medium failed to isolate organisms obtained by the ordinary procedure. Any comparison of results obtained by the routine mediums with those obtained by the K medium must include a consideration of the quantity of blood and of the quantity and quality of the mediums employed.

Ordinarily, 21 cc. of blood is used in the routine method for blood cultures. After the flask of K medium was substituted for the tomato flask, only 16 cc. of blood was taken for the routine mediums and only from 5 to 10 cc. (generally about 8 cc.), or half as much, was inoculated into the flask of K medium. Likewise considerably less medium was employed in the K flask than in the ordinary procedure. Still the increased accuracy represented in the four additional positive cultures when only nineteen of one hundred cultures were positive appears to be of sufficient significance to justify the importance of the larger quantities of blood and medium used in the laboratories of this hospital. It is possible, however, to compare the results obtained with the flask of K medium with those obtained in any one of the other flasks, as these were inoculated with only 5 cc. of blood. In that case one finds that whereas the flasks of K medium failed to grow organisms in four instances in which the routine mediums combined gave growth, the dextrose broth flask failed to grow organisms in only one instance, and the plain broth flask, in five instances. There were, furthermore, five instances in which one or more of the plates containing solid medium failed to grow organisms when a positive culture was obtained. Thus, considered as a single unit, the flask of K medium was inferior to the dextrose flask and somewhat superior to the plain broth flask.

There are, in addition, other advantages of the routine method, some of which were not brought out in this study. Thus it was found by Lichtman and Gross [6] that in a small percentage of cases which clinically appeared to be of rheumatic fever, nonspecific ulcerative colitis,[7] chronic cardiovalvular disease, rheumatoid arthritis, aplastic anemia, pernicious anemia, meningococcic meningitis, pyelitis, pyelonephritis, leukemia and nephritis, a nonhemolytic streptococcus was grown from the blood stream in fluid but not in solid medium owing to an insufficient number of organisms, as smaller amounts of blood are inoculated into the solid medium, and the mortality on solid medium is greater. Hence, unless the organisms in the blood stream are sufficiently numerous, no growth will be obtained on solid medium. This feature, as pointed out earlier by Libman,[8] has generally aided in distinguishing a transitory invasion of the blood stream by streptococcus from the bacteremia of subacute bacterial endocarditis, in which the organisms are generally sufficient to give growth in both fluid and solid mediums. Furthermore, the use of the K medium alone without solid mediums as employed in the routine method would provide great difficulty in isolation of the causative organisms when a mixed infection is present. Another objection is the longer period required with the use of only a Kendall flask before a given organism is isolated from the blood stream. With the routine method, it is often possible to determine the organism from the primary culture, i. e., without further subculture. This is particularly true when the organism is a streptococcus which appears on the blood plate. With the K medium, further subculture onto solid medium is necessary before identification. Finally, the greater cost and difficulty and the much longer time required for preparation of the medium seriously militate against its use in place of the mediums ordinarily employed.

Claims for the existence of filtrable forms of ordinary organisms as proposed by Kendall have been made also by a number of other investigators. Recently Hauduroy [9] summarized the evidence for invisible, filtrable forms of visible bacteria and discussed a number of such organisms. Since the experiments of Fontes [10] and of Vaudremer [11]

6. Lichtman, S. S., and Gross, Louis: Streptococci in Blood in Rheumatic Fever, Rheumatoid Arthritis and Other Diseases Based on a Study of 51,233 Consecutive Blood Cultures, Arch. Int. Med. **49**:1078 (June) 1932.

7. Crohn, B. B., and Schwartzman, G.: J. Lab. & Clin. Med. **14**:722 (May) 1929.

8. Libman, E.: Characterization of Various Forms of Endocarditis, J. A. M. A. **80**:813 (March 24) 1923.

9. Hauduroy, P.: J. de physiol. et de path. gén. **25**:254, 283, 522 and 537 1923.

10. Fontes, A.: Mem. Inst. Oswaldo Cruz **1**:51, 1909.

11. Vaudremer, A.: Compt. rend. Soc. de biol. **89**:80 (June 9) 1923.

the presence of such filtrable, invisible forms of the tubercle bacillus has been maintained. More recently Kahn and Torrey [12] described various forms of this organism forming a complete cycle.

In the blood cultures considered in this study, I sought first to determine the possibility of such filtrable, invisible forms being present in the blood of febrile patients in whose blood the routine cultures showed no growth, and second to determine whether ordinary organisms by repeated subculture in tubes of K medium could be converted into these invisible forms which would pass through a filter and reappear when cultivated on ordinary solid medium. In no instance did I succeed in obtaining such forms regardless of whether the original culture on K medium showed growth or not. This coincides with the findings recently reported by Craig and Johns,[13] who noted that B. typhosus, Corynebacterium diphtheriae, Staph. albus and Str. viridans grew poorly or were lost on subculture when grown on K medium, and when filtered and transferred to ordinary mediums, gave no growth. Of the nineteen positive cultures in the K flask, eight were lost on subculture. None of these reappeared after filtration and transfer to solid medium.

More interesting perhaps were the eleven cultures that remained viable through the three subcultures and up to the point of filtration. Four of these passed through the Berkefeld N filters not as invisible forms, but in their ordinary guise, clearly detectable on smear and on further culture. This becomes more significant with the detailed study of filtrability made by Varney and Bronfenbrenner [14] with various cultures in K medium. They showed that there was a greater incidence of passage of viable units from K cultures than from cultures on ordinary mediums, and that there are substances in the K medium which break down the efficiency of these filters, rendering them more permeable to bacterial suspensions made either in K medium, saline solution or broth when these suspensions are filtered just after passage of sterile K medium.

SUMMARY

1. One hundred and three routine blood cultures were made for seventy-seven patients suffering from a variety of febrile illnesses suggesting the presence of bacteremia. Simultaneously, flasks containing K medium were inoculated with blood from these patients.

12. Kahn, M. C., and Torrey, J. C.: Tr. Nat. A. Prev. Tuberc. **24**:264, 1928; Am. Rev. Tuberc. **18**:815 (Dec.) 1928.

13. Craig, C. F., and Johns, F. M.: Proc. Soc. Exper. Biol. & Med. **29**:661 (Feb.) 1932.

14. Varney, P. L., and Bronfenbrenner, J.: Proc. Soc. Exper. Biol. & Med. **29**:804 (April) 1932.

2. The K medium showed 4 per cent less positive results than the ordinary routine method. Compared with the individual flasks and plates used in the ordinary method, the flask of K medium showed slight inferiority to some and slight superiority to other individual units.

3. Other disadvantages were found in the difficulty and expense of preparing the medium and the greater time necessary before an organism could be identified.

4. Repeated subcultures from the original K flask failed to show any invisible, filtrable forms which could be converted to the ordinary state by transfer to solid medium as alleged by Kendall. There was no evidence in the cases studied to show that the clinical picture was due to a filtrable, invisible form of an organism which did not show itself on the ordinary mediums.

5. In several instances common organisms were found to pass through the Berkefeld filter, suggesting the possibility that the K medium may have had some influence in impairing the efficiency of the filter.

AN UNUSUAL BLOOD GROUP

MABLE M. WILHELM, B.A.
AND
EDWIN E. OSGOOD, M.D.
PORTLAND, ORE.

It was observed, in the course of blood grouping and matching, that certain bloods apparently belonging to group II did not match. In an attempt to find why these bloods did not match the serums were tested with known cell suspensions and some were found to be group IV (Moss). It was then discovered that the serum used as known group III agglutinated some group IV cells, and a thorough study of this serum was undertaken.

The agglutination reactions of this serum (III_1) were tested with eight group I, seventy-two group II, fifteen group III and a hundred group IV cell suspensions. The cells from our subject were tested with seven group III, three group I and several group II serums. The results are given in table 1. The method used in all agglutination tests was as follows: Two drops of serum were mixed on a clean slide with one drop of a cell suspension in a solution of 1 per cent sodium citrate in 0.85 per cent sodium chloride. The slides were kept at room temperature in covered petri dishes containing moistened filter paper to prevent drying. The slides were rotated to insure mixing and were examined at intervals. A result was not reported as negative until after examination at thirty minutes or more.

Note in table 1 that this group III_1 serum differs from typical group III serum in that it agglutinated 33 per cent of the fifteen group III cells examined and 47 per cent of the hundred group IV cells examined. The cells differ from typical group III cells in that they were agglutinated by 43 per cent of the seven group III serums tested. The presence of agglutination could be detected macroscopically. The extent of the agglutination would be graded 2 to 3 plus if the agglutination of group II cells is regarded as 4 plus. The appearance of the clumps is identical with that of the clumps of group II cells.

To prove further that this was an iso-agglutinin and not a pseudo-agglutinin, absorption experiments were done. The results of these experiments are summarized in table 2. The cells used for absorption

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From the Department of Medicine and the Outpatient Clinic Laboratory, University of Oregon Medical School, Portland.

were all agglutinated by this serum. It is evident that there are at least two types of group II cells. That corresponding to II_B in table 2 contains an agglutinogen reacting with the unusual agglutinin in this group III_1 serum as well as the usual agglutinogen reacting with group III serum. The other group II cells contain only the typical agglutinogen. The results shown in the table may be explained by the presence of a single extra agglutinin in this group III_1 serum and of a corresponding single agglutinogen occurring in some of the cells in each of

TABLE 1.—*Agglutination Reactions of Group III_1 Serum* *

Classifications			Serum				
Landsteiner	Jansky	Moss Cells	I	II	III	III_1	IV
AB	IV	I	0	+	+	+	+
A	II	II	0	0	+	+	+
B	III	III	0	+	0	+ (33% of cells)	+
		III_1	0	+	+ (43% of serums)	0	+
0	I	IV	0	0	0	+ (47% of cells)	0

* + = agglutination; 0 = no agglutination.

TABLE 2.—*Results of Absorption Experiments.*

	Serum III_1 Absorbed with Cells			
Cells	II_B	II_W	III_K	IV_M
II_B	0	+	+	+
II_W	0	0	+	+
III_K	0	+	0	0
IV_M	0	+	0	0

the three groups tested. It is probable that this agglutinogen could also be found in group I cells.

The serums were kept in the icebox, but no special precautions were taken to keep them sterile. Fresh serum of group III_1 was taken from time to time and duplicate experiments done. The agglutinating properties remained constant for several months.

When the agglutination reactions were carried out at 37 C., the agglutination with group IV cells was somewhat less marked, but still very definite.

Investigation of the family showed that the father belonged to group IV, the mother to group I, a sister to group II and a brother to group III. Neither the mother's nor the father's serum agglutinated the group IV cells which were agglutinated by the group III_1 serum. The

father's cells (group IV) were not agglutinated by the group III_1 serum. The brother's and the sister's blood were typical group III and II, respectively; neither their serums nor cells showed unusual reactions.

TABLE 3.—*Summary of Atypical Agglutination Reactions.*

Author	Number of Cases	Subgroup of Group	Atypical Reaction Serum Agglutinates Cells
Landsteiner and Witt: Proc. Soc. Exper. Biol. & Med. **21**: 389, 1924; J. Immunol. **11**: 221, 1926	2	I	All I, 75% II
Wiemer: Deutsches Arch. f. klin. Med. **156**: 305, 1927	?	I	Yes
Lauer: Ztschr. f. d. ges. gericht. Med. **11**: 264, 1928	?	I	Yes
Thomsen: Ztschr. f. Immunitätsforsch. u. exper. Therap. **57**: 301, 1928	4	I	?
Landsteiner and Levine: J. Immunol. **17**: 1, 1929	1	I (A_1B)	All IV and II_2
	1	I (A_1B)	All IV and some II_2
	1	I (A_2B)	Some II_1 and all I (A_2B)
Brem: J. A. M. A. **67**: 190 (July 15) 1916	1	II	Not I
Unger: J. A. M. A. **76**: 9 (Jan. 1) 1921	1	II	IV
Sucker: Ztschr. f. Hyg. u. Infektionskrankh. **102**: 482, 1924	1	II	II and I, not III
Thomsen: Ztschr. f. Immunitätsforsch. u. exper. Therap. **57**: 301, 1928	19	II	?
	1	II	Not III
Landsteiner and Levine: J. Immunol. **17**: 1, 1929	3%	II	12% II
	1	II_1	Some IV
	1	II_2	II_1
	4	II	Some IV and II
Meleney and co-workers: Am. J. M. Sc. **154**: 733, 1917	Occ.	III	Not II
Sucker: Ztschr. f. Hyg. u. Infektionskrankh. **102**: 482, 1924	1	III	* Not II and I
Guthrie and Huck: Bull. Johns Hopkins Hosp. **34**: 37, 80 and 128, 1923	4	III	Not all II
Thomsen: Ztschr. f. Immunitätsforsch. u. exper. Therap. **57**: 301, 1928	3	III	?
Meyer and Ziskovin: Med. Klin. **19**: 87, 1923	1	III	III
Landsteiner and Levine: J. Immunol. **17**: 1, 1929	2%	III	6% III
	6	III	Some III and IV
Ottenberg and Johnson: J. Immunol. **12**: 35, 1926	1	III	Some III and IV
Wilhelm and Osgood (1932)	1	III	Some III and IV
Beck: Ergebn. d. inn Med. u. Kinderheilk. **30**: 150, 1926	1	III	Some IV
Coca and Klein: J. Immunol. **8**: 477, 1923	1	IV	I after absorption with II and III cells
Unger: J. A. M. A. **76**: 9 (Jan. 1) 1921	6	IV	Some IV
Phillips: M. J. Australia **1**: 429, 1928	1	IV	Some IV
Landsteiner and Levine: J. Immunol. **17**: 1, 1929	5%	IV	10-20% IV
Thomsen: Ztschr. f. Immunitätsforsch. u. exper. Therap. **57**: 301, 1928	6	IV	?
	2	IV	Not III
	1	IV	Not II

In table 3 are summarized the subgroups which have so far been recognized. Note that the case of Meyer and Siskovin and the case of Beck, while incompletely studied, probably belong to the same subgroup as the case here reported. Ottenberg and Johnson have reported one case and Landsteiner and Levine six cases (disregarding the ±

reactions) which seem identical with our case. The case of Ottenberg and Johnson is unique in that a fatality resulted when a group III recipient was transfused with blood from a group III donor whose serum agglutinated the recipient's cells. Landsteiner and Levine [1] have studied the heredity of the agglutinable properties of red cells to exceptional serums and find there is an inheritance of such properties and racial differences in their distribution.

The occurrence of subgroups is of great clinical importance, and it is surprising that texts giving the technic of the selection of donors for transfusions seldom mention the errors which may result from the occurrence of subgroups. By using this group III_1 serum for typing, some group IV bloods were classed as group II and some group III bloods were classed as group I. Fatal accidents would certainly have occurred had not direct matchings been done in addition. A fatal accident would be likely to occur if our subject were to be given a transfusion with blood from certain group IV (universal) donors, or even if she were a donor or recipient in a transfusion with another person in her own group.

The precautions necessary to avoid such accidents are evident. Both typing and direct matching should always be carried out. Serum selected for use in typing should be tested against a number of cell suspensions from each of the blood groups to be certain that it has a high titer and gives no atypical agglutination. When direct matching of bloods supposedly from the same group gives agglutination, the serums should be tested with cell suspensions from each group. Universal donors should not be used without direct matching of the recipient's serum with the donor's cells.

SUMMARY

1. A subgroup of group III is described which is characterized by a serum which agglutinates 33 per cent of group III cells and 47 per cent of group IV (Moss) cells, and by cells which are agglutinated by 43 per cent of group III serums.

2. Previously reported subgroups are summarized.

3. Precautions necessary to prevent accidents are outlined.

1. Landsteiner, K., and Levine, P.: On the Inheritance and Racial Distribution of Agglutinable Properties of Human Blood, J. Immunol. **18**:87, 1930.

CLINICAL SIGNIFICANCE OF LATENT PULMONARY TUBERCULOSIS

F. MAURICE McPHEDRAN, M.D.
AND
EUGENE L. OPIE, M.D.
NEW YORK

A significant advance in knowledge of tuberculosis has come from recognition of the occurrence of grave, often progressive, disease that has not undermined health, has produced no evident symptoms and is unassociated with physical signs demonstrable by the usual methods of physical examination. Nevertheless, the fundamental importance of this latent tuberculosis as a forerunner of clinically manifest disease is not universally accepted. Many clinicians have been unwilling to admit that progressive tuberculous lesions are evident in roentgenographic films before the disease has produced any symptoms or physical signs. Roentgenographic examination often reveals the anatomic characters of tuberculous lesions before they have produced any functional disturbances demonstrable by existing methods. Progress in the early diagnosis of pulmonary tuberculosis by means of procedures available today is chiefly dependent on wider recognition of the value of technically adequate roentgenographic examination of the chest.

Some clinicians and roentgenologists find it difficult to separate latent from arrested tuberculosis because the lesions concerned may be indistinguishable by their anatomic characters as defined by x-ray films. Inquiry will usually determine if there have been symptoms of respiratory disease referable to pulmonary tuberculosis. The distinction between latent and arrested tuberculosis has obvious significance from the point of view both of the patient and of public health.

In 1926, we [1] described the numerous latent tuberculous lesions that we observed in members of families living in contact with tuberculosis and the occasional lesions found in those with no history of contact with the disease. In the present publication we describe instances of latent pulmonary tuberculosis many of which have been observed during from six to eight years.

From the Henry Phipps Institute, University of Pennsylvania, Philadelphia.

1. Opie, E. L., and McPhedran, F. M.: Am. Rev. Tuberc. **14**:347, 1926.

In the following classification of latent tuberculous lesions of the lungs are enumerated those that are distinguishable by roentgenographic examination of the chest:

Latent tuberculous lesions of the lung (of first infection or childhood type)
- (*a*) Soft (appearing as spots or as flocculent shadows)
- (*b*) Strandlike (healing or healed)
- (*c*) Calcified nodules of the lung (healing or healed)

Tuberculosis of tracheobronchial lymph nodes
- (*a*) Massive caseous tuberculosis
- (*b*) Calcified tuberculosis (healing or healed)

Latent apical tuberculosis (of reinfection or adult type)
- (*a*) Scant lesions appearing below the posterior part of the second rib
- (*b*) Lesions occupying approximately one half or more of the apex above the clavicle as seen in x-ray films
- (*c*) Lesions extending from above below the clavicle and not exceeding those of minimal tuberculosis
- (*d*) Lesions equivalent in extent or character to those of moderately advanced tuberculosis

It is noteworthy that in the classification are defined the lesions recognizable with present methods in x-ray films, and to avoid controversial questions no attempt is made to define exactly the pathologic picture of the lesions concerned.

TUBERCULOUS INFILTRATION OF FIRST INFECTION OR CHILDHOOD TYPE

Early lesions of the parenchyma of the lung referable to tuberculous infiltration cast shadows on the roentgenographic films that occur in spots and cause a clouded or flocculent appearance (soft infiltration). In films of the chest the density of spots and their proximity to one another are rough indexes of invasion of air-containing alveolar, by solid tuberculous, tissue. Patches of tuberculous pneumonia or confluent tubercles produce similar shadows in roentgenographs of excised tuberculous lungs. Opaque, homogeneous shadows of considerable extent indicate solidification of lung tissue referable to a pneumonic process. Roentgenographic studies have emphasized the frequency with which extensive tuberculous infiltration of the lung in children undergoes resolution with complete disappearance of homogeneous density or its replacement by strandlike shadows that represent fibrous tissue. Hence, tuberculous lesions in young children usually appear as soft spots, whereas in older children they are strandlike. The transition from the former to the latter is frequently observed (table 1).

Strandlike infiltration was not found in any of the Negro children at the time when they first came under observation.

Latent infiltration of the lung that was seen as soft spots in the films of the chest of white children became clinically manifest tuberculosis within an average period of seven months after its recognition, the shortest being two weeks and the longest one year and three months. The disease was arrested in all of these seven cases after an average

TABLE 1.—*Latent Tuberculous Infiltration of the Lung of First Infection or Childhood Type*

	Age	Number With Infiltration When First Seen	Number That Later Became Strandlike and Developed		Number That Developed into Clinically Manifest Pulmonary Tuberculosis	Per Cent That Developed into Clinically Manifest Pulmonary Tuberculosis
			No Recognizable Calcification of Tracheobronchial Lymph Nodes	Recognizable Calcification of Tracheobronchial Lymph Nodes		
White						
Soft infiltration	0-4	11	2	6	2	
	5-9	6	3	..	1	
	10-14	3	3			
	15-19					
	20+					
Soft infiltration with massive caseous tuberculosis of tracheobronchial lymph nodes	0-4	2	..	1	1	35
	5-9					
	10-14					
	15-19					
	20+					
Soft infiltration with calcified tracheobronchial lymph nodes	0-4	2	..	1	1	
	5-9	6	..	4	2	
	10-14					
	15-19					
	20+					
Strandlike infiltration with or without calcified tracheobronchial lymph nodes	0-4					
	5-9	3				
	10-14	3				
	15-19	1				
	20+	1				
Negro						
Soft infiltration	0-4	2	2			
	5-9					
	10-14	1				
	15-19					
	20+	1	1			
Soft infiltration with massive caseous tuberculosis of tracheobronchial lymph nodes	0-4	2	..	1	1	38.4
	5-9	1	..	..	1	
	10-14					
	15-19	1	..	..	1	
	20+					
Soft infiltration with calcified tracheobronchial lymph nodes	0-4	1	..	1		
	5-9					
	10-14	1				
	15-19	1	..	..	1	
	20+					

period of three years and six months (minimum two years; maximum, five years and a half) following recognition of the lesion.

After recognition of similar lesions in Negro children, clinically manifest tuberculosis made its appearance after an average period of four months (least one month and greatest six months). Death occurred in one instance seven months after the lesion was first discovered. The three remaining children were under observation from

eleven months to two years and eight months, and the disease was still present. Hence, the transition to clinically recognizable disease occurs more rapidly, and the probable outcome is more unfavorable, in Negroes than in white persons.

In nineteen instances in white children, latent infiltration represented in roentgenographs by soft spots later diminished in extent and assumed a strandlike character in the film. This change was observed after an average period of two years and three months. In five instances the infiltration was accompanied by recognizable calcified tuberculosis of tracheobronchial lymph nodes when first seen, and in six more calcification of lymph nodes had made its appearance at the time when the infiltration had become strandlike.

In Negroes, soft infiltration had assumed a strandlike character in five instances after an average period of two years and three months. In one of these cases massive caseous tuberculosis became calcified and in another calcification of tracheobronchial lymph nodes became evident in the film, although during the preceding caseation the nodes had not been large enough to be demonstrable by the x-rays.

With the transition of soft spots or flocculent shadows into inconspicuous strands with or without manifest disease, it is evident that the tuberculous lesion has undergone more or less resolution. The following are examples of extensive resolution demonstrated by roentgenographic films:

Catherine, a white girl, aged 11 months, was exposed to tuberculosis in her mother, who had tubercle bacilli in her sputum. When the child was first seen there was consolidation of the lower part of the right upper lobe varying in density over an area 3.5 cm. across. After nine months the area of consolidation was only 2.5 cm. across, and there was calcification in spots (McPhedran,[2] fig. 5). After an additional four years and three months, a few strands and some calcified spots replaced the former opacity.

Angelina, a white girl, aged 1 year, was exposed to pulmonary tuberculosis in her mother, who had tubercle bacilli in her sputum. There was a homogeneous opaque consolidated area occupying the upper part of the left upper lobe, 4 by 3 cm. After six months cough appeared; the density of consolidation had evidently diminished, and scattered light spots were seen over the same area. After an additional one year and four months, symptoms had disappeared and the lesion was reduced to a calcified nodule and a few strands. A lymph node at the hilus of the lung had undergone calcification. Finally, after a year more the roentgenogram showed light strands and a calcified nodule in an area 3 cm. across together with a large calcified tracheobronchial lymph node.

The observations that have been cited show that homogeneous tuberculous consolidation may gradually resolve and its shadow diminish in the film so that a few strandlike markings, presumably caused by newly

2. McPhedran, F. M.: Am. Rev. Tuberc. **20**:532, 1929.

formed fibrous tissue, with occasionally a few calcified spots, alone remain as scars of the healed lesion. In some instances roentgenographs show that calcification, presumably of caseous foci, has simultaneously occurred in adjacent lymph nodes.

Strandlike infiltration of the lung was found at the first roentgenographic examination in eight instances in white persons (table 1) and in no instances in Negroes. In thirty white persons with soft infiltration, the lesion became strandlike in twenty-six (86.7 per cent), in seven of whom clinically manifest tuberculosis developed that was later arrested. In eleven Negroes, soft infiltration became strandlike in five (45.5 per cent), and in none of these was tuberculosis clinically manifest.

MASSIVE CASEOUS TUBERCULOSIS OF TRACHEOBRONCHIAL LYMPH NODES

Caseous lesions of lymph nodes are recognizable only when they are associated with such massive enlargement that some part of the oval outline of the node is clearly recognizable against the pulmonary field either at one side of the mediastinum or in the hilus of one or the other lung. Small caseous foci are not recognizable in roentgenographic films until they have been impregnated with calcium salts.

Massive caseous tuberculosis of lymph nodes was recognized in association with clinically manifest pulmonary tuberculosis in three white persons, two of whom died, and in ten Negroes, three of whom died. Of the latter, three others had far advanced tuberculosis when last seen.

Table 2 contains all instances of latent massive caseous tuberculosis of tracheobronchial lymph nodes that were recognized. It shows that latent massive caseous tuberculosis has grave significance. In five instances it was associated with tuberculous infiltration of the lung, and in three of these, clinically manifest disease later developed. Of six instances in which massive caseous tuberculosis of tracheobronchial lymph nodes was unaccompanied by other lesions when first seen, clinically manifest pulmonary tuberculosis made its appearance in two. We have obtained no evidence that the tuberculous lesions of the lymph nodes produce recognizable symptoms or physical signs.

The lesion of the lymph nodes underwent calcification in four instances.

Massive caseous tuberculosis of tracheobronchial lymph nodes has occurred more frequently in Negro than in white children, and in the former it is evidently more likely to appear in adolescence. During the period of the present study, massive caseous tuberculosis accompanied clinically manifest tuberculosis in thirteen instances. Of these,

three were in white persons, aged 2 months, 10 and 20 years, respectively, and ten were in Negroes from 7 months to 33 years of age, seven being 12 or more years of age.

TUBERCULOSIS OF TRACHEOBRONCHIAL LYMPH NODES WITH CALCIFICATION

To obtain information concerning the potential significance of tracheobronchial tuberculosis with calcification of the lesion, it is essential to separate instances of tracheobronchial tuberculosis unaccompanied by pulmonary lesions from those in which at the first observation the tracheobronchial tuberculosis is associated with latent infiltration of the lung substance of either first infection (childhood type) or of reinfection (latent apical or adult type). We have no evidence that partially or completely calcified lesions of tracheobronchial lymph nodes produce recognizable symptoms or physical signs.

TABLE 2.—*Latent Massive Caseous Tuberculosis of Tracheobronchial Lymph Nodes*

	Sex	Age When First Seen, Years	Associated Pulmonary Lesion When First Seen	Subsequent Change in Lymph Nodes	Subsequent Change in Pulmonary Lesion	Comment
White						
803,R	F	3	Soft infiltration	Calcified	Strands	
787,M	F	4 3/12	Soft infiltration	.....	Manifest pulmonary tuberculosis	
954,A	M	15	.....	.....	.....	One examination only
Negro						
891,G	M	1 7/12	Soft infiltration	.....	Manifest pulmonary tuberculosis	Observed one week only
828,H	F	4	Soft infiltration	.....	Manifest pulmonary tuberculosis	Died
124,G	M	6	Soft infiltration	Calcified	Strands	
737,V	F	7	.....	Calcified		
281,T	F	9 7/12	.....	.....	Manifest pulmonary tuberculosis	
941,C	F	12	.....	Calcified		
896,N	F	12	.....	.....	.....	One examination only
221,R	F	15	.....	.....	Manifest pulmonary tuberculosis	

Table 3 shows the frequency with which clinically manifest pulmonary disease developed in persons with calcified tracheobronchial tuberculosis with and without pulmonary lesions. In persons with tracheobronchial tuberculosis recognized by the presence of calcification, clinically manifest disease develops only in a small percentage of cases. When the lesion was associated with no recognizable infiltration of the

lung, the incidence of subsequent manifest tuberculosis was 1.8 per cent in white people, and 3.1 per cent in Negroes. In all save one of these instances the disease made its appearance in persons in contact with a patient with tuberculosis with tubercle bacilli in the sputum. When tracheobronchial tuberculosis with calcification is accompanied by infiltration of the lung, the percentage of those who develop clinical tuberculosis is much greater and approximates that following infiltration

TABLE 3.—*Frequency with Which Persons with Latent Tuberculosis of Tracheobronchial Lymph Nodes Develop Clinically Manifest Tuberculosis*

Lesion When First Seen	Age, Years	Number with Tracheo-Bronchial Tuberculosis	Number That Changed to Clinically Manifest Tuberculosis	Per Cent That Changed to Clinically Manifest Tuberculosis
White				
Calcified tracheobronchial tuberculosis alone	0-4	17	1	1.8
	5-9	52	0	
	10-14	76	2	
	15-19	26	..	
	20-39	47	1	
	40+	18	..	
Calcified tracheobronchial tuberculosis with infiltration of first infection	0-4	3	1	33.1
	5-9	7	2	
	10-14	2	..	
	15-19	1	..	
	20-39	..	..	
	40+	..	..	
Calcified tracheobronchial tuberculosis with latent apical tuberculosis	0-4	..	..	18.7
	5-9	..	..	
	10-14	3	1	
	15-19	4	1	
	20-39	9	1	
	40+	12	..	
Negro				
Calcified tracheobronchial tuberculosis alone	0-4	..	..	3.1
	5-9	8	..	
	10-14	10	..	
	15-19	5	1	
	20-39	9	..	
	40+	6	..	
Calcified tracheobronchial tuberculosis with infiltration of first infection	0-4	1		
	5-9	..		
	10-14	1		
	15-19	1		
	20-39	..		
	40+	..		

Note.—There were no instances in which Negroes with calcified tracheobronchial and associated latent apical lesions developed clinically manifest disease.

with no demonstrable tracheobronchial lesion. The frequency with which those with tracheobronchial tuberculosis and latent apical lesions develop clinically manifest disease is also much greater (18.7 per cent) than when only tracheobronchial lesions occur and closely approximates the figure for all latent apical lesions (20 per cent).

LATENT APICAL TUBERCULOSIS

Latent apical lesions have been divided into the following groups defined by their anatomic extent in order to measure their potential significance:

1. Definite but scant lesions seen immediately below the lower border of the posterior part of the second rib.

2. Well defined lesions occupying approximately half or more of the apex above the clavicle. It is assumed that in the roentgenograph the shadow of the mesial part of the clavicle lies on that of the posterior part of the fourth rib.

3. Lesions extending from above below the clavicle and not exceeding those of clinically manifest minimal tuberculosis, that is, limited to the pulmonary field above the level of the upper margin of the second chondrosternal junction and the fifth vertebral spine. When a cavity or dense consolidation is present, the lesion is placed in group 4.

TABLE 4.—*Frequency with Which Persons of Various Ages with Latent Apical Tuberculosis Have Developed Clinically Manifest Tuberculosis*

	Extent of Lesion	Age	Number With Latent Apical Lesions	Number That Developed Manifest Tuberculosis	Per Cent That Developed Manifest Tuberculosis
Group 1:	Scant lesions	10-14	6	2	5.7
		15-19	4	0	
		20-39	25	0	
		40+	6	0	0.0
Group 2:	Approximately half or more of apex above clavicle	10-14	7	3	25.0
		15-19	8	2	
		20-39	17	3	
		40+	16	1	6.2
Group 3:	Equivalent to minimal tuberculosis	10-14	1	0	47.8
		15-19	11	7	
		20-39	11	4	
		40+	12	1	8.3
Group 4:	Equivalent to moderately advanced tuberculosis	10-14	2	1	50.0
		15-19	1	1	
		20-39	3	1	

4. Moderately advanced latent lesions occupying an area exceeding that just defined and equivalent to moderately advanced, clinically manifest tuberculosis.

In view of the varying character of tuberculous infection at different ages, latent lesions have been grouped by age (table 4) in order to determine the frequency with which manifest tuberculosis makes its appearance in each age group.

Table 4 shows that latent apical lesions more frequently develop into manifest disease before than after 40 years of age. After this age latent lesions appear to have assumed a considerable degree of stability, although in a small proportion of cases (approximately 6 per cent) the disease previously latent becomes manifest. The table further shows that in persons between 10 and 40 years old, the probability that the lesion will seriously impair health increases with its extent at the time of observation. Of the smallest recognizable lesions (group 1) only a

few (5.7 per cent) develop into clinically manifest disease, whereas of more conspicuous lesions, limited to the apex above the clavicle, one fourth develop into clinically recognizable disease. Of all lesions that extend below the clavicle, approximately one half become manifest, and the potential significance of this lesion is evidently so great that it should receive the same treatment as clinically manifest tuberculosis until repeated roentgenographic examination has demonstrated that it is not progressive.

The average time between the discovery of latent apical tuberculosis and the development of clinically manifest disease was approximately one year and four months, the longest time being five and a half years, and the shortest, two months.

In seven of the twenty-six persons whose latent apical lesion became manifest disease, tubercle bacilli appeared in the sputum, and five died.

The number of latent apical lesions in Negroes has been so small that tabulation of them has been omitted. The total number was fourteen, and in two of them clinically manifest tuberculosis developed. These two patients when first seen had lesions of groups 2 and 3.

CONCLUSIONS

The early diagnosis of pulmonary tuberculosis is in a large part dependent on the recognition of lesions that have not impaired health (latent pulmonary tuberculosis).

Soft infiltration of the lung referable to a first infection with tuberculosis (childhood type) in approximately two thirds of all instances undergoes resolution and healing with formation of a fibrous or calcified scar and is accompanied by no evident symptoms or physical signs, but in 35 per cent of cases clinically manifest tuberculosis makes its appearance. In white children this disease usually becomes arrested, but in Negro children it more frequently pursues an unfavorable course.

Massive caseous tuberculosis of tracheobronchial lymph nodes is infrequently recognizable in roentgenographs, and when not associated with demonstrable pulmonary infiltration is seldom if ever accompanied by demonstrable symptoms or physical signs; with obvious development of a pulmonary lesion, it is followed by clinically manifest pulmonary tuberculosis in about one third of the cases. It is found oftener in Negroes than in white persons, and in the former occurs more frequently during adolescence.

Tracheobronchial lymph node tuberculosis with recognizable calcification is with few exceptions a healed or healing lesion, and its recognition if unaccompanied by tuberculous infiltration of the lung when first seen is seldom (in only 2 or 3 per cent of cases) followed by manifest pulmonary disease.

The potential significance of latent apical tuberculosis varies with age and the anatomic extent of the lesion. After 40 years of age these lesions are usually stationary.

In younger persons scant lesions projecting below the border of the second posterior rib are followed by clinically manifest tuberculosis in approximately 6 per cent of instances.

Of latent apical lesions that occupy approximately one half or more of the apex above the level of the clavicle, one fourth develop into clinically manifest disease.

Of latent apical lesions that extend from above below the clavicle, approximately half become clinically manifest tuberculosis.

Persons less than 40 years of age with latent apical lesions scattered over an area approximating one half of the apex above the clavicle or with more extensive lesions, even though they are in apparently good health, should receive the treatment of clinically manifest pulmonary tuberculosis until repeated roentgenographic examinations have shown that the lesion is not progressive.

FUNCTION OF THE LIVER

AN APPRAISAL OF THE MODIFIED DEXTROSE TOLERANCE TEST

HENRY T. RICKETTS, M.D.
CHICAGO

In 1930, Althausen, Gunther, Lagen and Kerr [1] described a modified dextrose tolerance test, which they offered as an index of the metabolic function of the liver. The technic of this test, performed on patients who had been for several days on a regular hospital diet, was as follows:

1. Estimation of blood sugar during fasting was made in the morning.
2. The patient was then given 20 units of insulin.
3. Twenty minutes later, the patient was given 50 Gm. of dextrose in 500 cc. of water by mouth, followed by 1,000 cc. of water by mouth.
4. Blood sugar determinations were made at one-half hour, one hour, two hours and three hours after the ingestion of the dextrose and water.

These authors observed that in ten patients without evidence of hepatic disease, the average of the blood sugar curves resulting from this test at no time fell below the fasting level, but that in patients who gave clinical evidence of hepatic insufficiency, there was a terminal fall in blood sugar to a point considerably below the fasting level, often accompanied by symptoms of hypoglycemia. This test was based on the hypothesis that "in normal persons the dextrose ingested during the test seems to be polymerized to glycogen, and in return released as dextrose with sufficient rapidity to counteract impending hypoglycemia, whereas in patients with hepatic disease, this process is sufficiently slowed to permit of reaching abnormally low blood sugar levels." They placed the dividing line between normal and abnormal responses at 70 mg. of sugar per hundred cubic centimeters of blood. They tested sixty-four patients and found, after eliminating certain cases which were unsatisfactory because of complications, that there was a 91 per cent agreement between the modified dextrose tolerance test and the rose bengal dye test of hepatic function.

In 1931, the senior author, Althausen,[2] reported the application of this test, together with the rose bengal test, in five cases of toxic

1. Althausen, T. L.; Gunther, L.; Lagen, J. B., and Kerr, W. J.: Modification of the Dextrose Tolerance Test as an Index of the Metabolic Activity of the Liver, Arch. Int. Med. **46**:482 (Sept.) 1930.

2. Althausen, T. L.: Functional Aspects of Regenerated Liver Tissue, Arch. Int. Med. **48**:667 (Oct.) 1931.

cirrhosis of the liver. In three of these cases the diagnosis was proved by autopsy or biopsy. In all instances in which the determinations were made in the chronic stage of the disease, he found by this means a normal carbohydrate metabolism in the face of marked retention of the rose bengal dye in the blood stream. Since in the first paper a close correlation between the carbohydrate and the dye tests had apparently been demonstrated in other forms of hepatic disease, it was concluded that the discrepancy between these tests in toxic cirrhosis constituted a basis for the clinical diagnosis of this disease. The simultaneous occurrence of normal hepatic carbohydrate metabolism and marked impairment of excretory function may be explained, says the author, by the pathologic anatomy and physiology of toxic cirrhosis. Anatomically, this condition is characterized by isolated nodules and areas of regenerated, usually bile-stained hepatic parenchyma. These areas, because they consist of normal cells and possess an adequate blood supply, are able to carry on carbohydrate metabolism in a normal fashion, but because they have no connection with the biliary tree, they are unable to perform the normal excretory functions.

In a critical review of these contributions, it is hard to escape the conclusion that the validity of the modified dextrose tolerance test in hepatic disease of any nature depends entirely on the question of whether or not persons with normal livers always respond to the test in the same way—i. e., by the maintenance of the blood sugar throughout the procedure at a level above 70 mg. per hundred cubic centimeters (the critical level as given by Althausen and his collaborators). The present study was undertaken in an attempt to answer this question conclusively.

METHODS

The modified dextrose tolerance test was performed on fourteen subjects. Of these, four were considered unquestionably normal so far as the liver was concerned; six gave a history suggesting possible damage to the liver at some earlier date, but presented at the time of examination no symptom or sign of hepatic disease, and four gave frank evidence of an existing hepatic pathologic process. The concern of this paper lies chiefly in the normal and probably normal cases, but the abnormal have been included as a matter of interest.

The technic followed in the test was identical with that used by Althausen, Gunther, Lagen and Kerr.[1] For several days prior to the test the patients had been either on a regular hospital diet or, because of the nature of the particular illness, on a special diet, both of which contained from 250 to 300 Gm. of carbohydrate. At 9:00 a. m., with the patient in a fasting condition, blood was drawn for the determination of sugar. At 9:10, the patient was given 20 units of insulin hypodermically. At 9:30, the patient ingested 50 Gm. of dextrose in 500 cc. of water, followed by 1,000 cc. of water. Samples for blood sugar determinations were drawn at 10:00, 10:30 and 11:30 a. m., and at 12:30 p. m. If signs or symptoms of hypoglycemia supervened at any time, a sample of blood was

taken, and the test was immediately terminated by the administration of orange juice and sugar by mouth.

The samples of blood sugar were in practically all instances transferred at once to the chemical laboratory, where analysis was begun before intrinsic chemical changes might occur. The analyses, made through the courtesy of Dr. Dorothy Gaston, were based on the method described by Folin in 1929 for determining blood sugar [3] and on the tungstate sulphate filter method,[4] determinations being made on the unlaked blood filtrate. Emphasis should be laid on the fact that, because some of the nonsugar-reducing substances are eliminated, the values for blood sugar obtained by these methods are lower than those given by the older analytic procedures, normal values being from 60 to 90 mg. per hundred cubic centimeters. Seventy milligrams per hundred cubic centimeters was the critical level decided on by Althausen and his co-workers, below which hypoglycemia was considered to exist. This is about 10 points below the lower limit of normal blood sugar as considered by most authors (80 mg.).[5] In order that the results here presented may be compared with those under discussion, a value 10 points below the lower limit of the normal (60 mg.) as given by the newer method of analysis has been chosen, giving a critical level of 50 mg. That this figure is not too high is borne out by the fact that all patients showing blood sugar of less than 50 mg. per hundred cubic centimeters exhibited signs and symptoms of hypoglycemia, such as hunger, pallor, sweating, drowsiness and tachycardia.

Because of the lack of agreement among various authors as to the value of dye tests of hepatic function, it was not deemed worth while to perform these in the normal and "probably normal" cases. The bromsulphalein intravenous dye test was done only in the four cases of outspoken disease of the liver. As has been pointed out, these cases are included here as a matter of interest, and for the sake of comparison, the main issue being the response of persons without hepatic disease to the modified dextrose tolerance test.

DATA

The accompanying table and chart are divided into three groups. Group I includes those cases in which no evidence of hepatic disease could be obtained from the history or from physical examination. All these patients were being treated for functional disorders of the gastro-intestinal tract, and in none was there any evidence of organic disease. In case 1, the modified dextrose tolerance test gave indeterminate results. Because the patient complained of "feeling queer" and had a cold, clammy skin at the end of two hours, the test was prematurely terminated, although the blood sugar did not fall below 55 mg. All the other patients of this group experienced a decided drop in blood sugar, and presented unmistakable clinical manifestations of hypoglycemia.

3. Folin, Otto: Two Revised Copper Methods for Blood Sugar Determination, J. Biol. Chem. **82**:83 (April) 1929.

4. Folin, Otto: Unlaked Blood as a Basis for Blood Analysis, J. Biol. Chem. **86**:173 (March) 1930.

5. McClellan, W. S., and Wardlaw, H. S. H.: Hypoglycemic Reactions Following Glucose Ingestion, J. Clin. Investigation **11**:513 (May) 1932.

Summary of Clinical Data and Tests of Hepatic Function

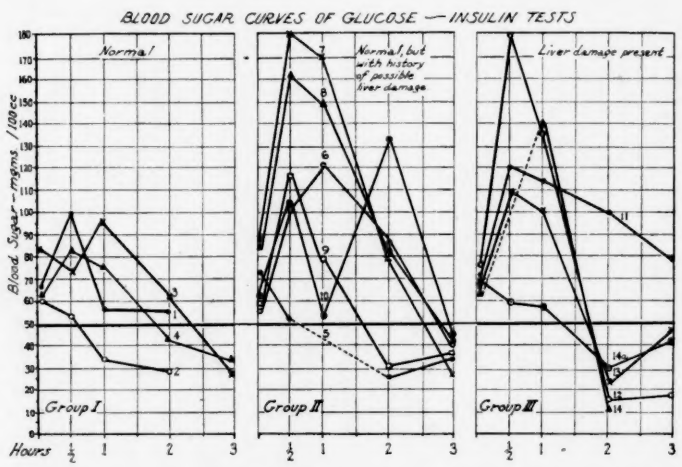
Case Number	Age	Sex	Diagnosis	Significant Physical Findings	History of Possible Hepatic Damage	Dextrose-Insulin Test *					Percentage of Dye Retained		Comment
							Blood Sugar						
						Shock	F	½ Hr.	1 Hr.	2 Hr.	3 Hr.	½ Hr.	1 Hr.	
					GROUP I									
1	46	F	Chronic functional colitis	General abdominal tenderness	None	?	66	99	57	55	..	..	..	
2	30	F	Malnutrition; chronic functional colitis	None	None	+	61	53	34	28	..	..	..	
3	29	F	Cardiospasm	None	None	+	83	73	96	67	27	..	..	
4	56	F	Migraine; cathartic colitis	None	None	+	63	83	75	42	33	..	..	
					GROUP II									
5	27	F	Chronic functional colitis; nervous vomiting	Highly nervous; abdominal scars; general abdominal tenderness	Cholecystectomy at 19	+	73	52	..	25	34	..	..	
6	34	F	Chronic sinusitis; chronic cystitis and pyelitis	None	1 glass port wine daily	0	55	102	122	85	40	..	..	
7	58	M	Duodenal ulcer with moderate stenosis; inactive pulmonary tuberculosis	Nervousness; subcapsular râles; lower abdominal and epigastric tenderness	Painless jaundice at 32	+	85	181	169	82	26	..	..	
8	44	M	Duodenal ulcer	Abdominal scars	Cholecystectomy; no jaundice	+	85	162	148	84	42	..	..	
9	23	M	Duodenal ulcer with moderate stenosis	Cardiac systolic murmur; epigastric tenderness and tenderness in right lower quadrant	Alcohol at rare intervals	+	58	116	79	30	36	..	..	

10	44	F	No organic disease	Tender right lower quadrant and right upper quadrant	Moderate pain in right upper quadrant without jaundice	+	62	102	53	133	43	..	..	Roentgenogram of gallbladder normal; blood sugar specimens at 1 hr. and 2 hrs. mixed in laboratory?		
					GROUP III											
11	66	M	Carcinoma of pancreas	Jaundice; mass in right upper quadrant; enlarged firm, smooth liver; spleen not palpable		0	71	120	114	99	78	10-20	0	Diagnosis confirmed at operation		
12	52	F	Atrophic cirrhosis with jaundice; duodenal ulcer	Jaundice; liver enlarged, hard, nodular; spleen palpable; anemia		+	75	179	135	15	17	0	0	Diagnosis confirmed grossly at operation; died later of pneumonia; no autopsy		
13	39	M	Syphilitic hepatitis	Slight icterus; enlarged, hard, nodular liver; enlarged, firm spleen; ascites; Wassermann and Kahn tests ++++	Alcohol at occasional intervals	+	66	109	100	23	47	10	5	Improving under antisyphilitic therapy		
														Gm. Galactose		
14	39	M	Syphilis (late) of central nervous system; arsphenamine hepatitis	Jaundice; marked hepatic enlargement—soft; spleen not palpable	Arsenical antisyphilitic treatment for 1½ years; last treatment five weeks before admission		..	...	...	...	..	80	70	Five Hrs.† ...	Date 12/23/31	Comment Recovered
							..	...	...	...	..	..	..	8.0	12/26/31	
						+	63	...	140	11	..	..	..	...	12/29/31	
							..	...	...	...	..	20	10	...	1/ 2/32	
							..	...	...	...	..	20	10	...	1/ 5/32	
							..	...	...	...	..	..	..	6.0	1/ 6/32	
						+	65	59	57	29	42	..	..	3.4	6/ 3/32	

* Hypoglycemic shock present, +; absent, 0; questionable, ?. Values for blood sugar are given as mg. per hundred cubic centimeters.

† The table shows the number of grams of galactose excreted in the urine during a period of five hours after the ingestion of 40 Gm. of this substance.

Group II consists of patients who gave a history of possible hepatic damage at an earlier date, but who, at the time of this study, were being treated for conditions in no recognized way related to the liver, and who gave no evidence of disease of the liver. On examination of the factors listed as possibly having produced previous hepatic injury, it seems unlikely that most of them per se could have caused serious dysfunction at any time, and even less likely that they could still be cogent in affecting any test of hepatic function. In case 5, the patient had had a cholecystectomy eight years before; in case 6, the patient was accustomed to taking one glass of port wine daily; in case 7, the patient had had painless jaundice twenty-six years before; in case 8, the patient had had a cholecystectomy with no history of jaundice; in case 9, the patient had indulged rarely in alcohol; in case 10, the patient complained of moderate pain in the right upper quadrant



Blood sugar curves obtained by dextrose-insulin tests. The horizontal line at the level of 50 mg. per 100 cubic centimeters represents the critical level for normal, below which hypoglycemia is considered to exist. Figures near curves indicate case numbers. A second determination made five months after *14* on the same patient is represented by *14a*. Broken lines connect points between which one blood sugar sample was omitted.

but had never had colic or jaundice, and a roentgenogram of the gallbladder showed normal visualization without stone. Since, however, no one can say with certainty that such factors have not produced some degree of parenchymal change, these cases are grouped separately, though it is believed that they may be classed as normal so far as intrahepatic physiology is concerned. All, without exception, showed chemical and clinical evidence of hypoglycemia.

Group III includes those cases in which frank hepatic disease was present. Jaundice and enlargement of the liver were present in all. The patient in case 11 had a carcinoma of the head of the pancreas with marked jaundice, yet showed no retention of dye in the blood stream at the end of an hour, and was the only patient who did not respond to the dextrose-insulin test by a drop in blood sugar. In case 12, the condition was diagnosed as atrophic cirrhosis of the liver and duodenal ulcer. The diagnosis was confirmed at operation. The patient was jaundiced and had an enlarged, hard, finely nodular liver, an enlarged spleen and secondary anemia. This case is of interest in that it showed marked hypoglycemia by the modified dextrose tolerance test, but no retention of bromsulphalein in the blood stream even at the end of half an hour. Althausen, in his cases of toxic cirrhosis, described exactly the opposite situation—namely, a normal reaction to the carbohydrate test and an abnormal reaction to the dye test. In case 13, in which the condition was diagnosed as syphilitic hepatitis, slight icterus, an enlarged, hard, nodular liver, a large firm spleen and ascites were present. The blood gave a positive reaction to the Wassermann and Kahn tests. This case is similar to the preceding one in showing, though to a lesser degree, a hypoglycemic reaction with an almost normal reaction to the bromsulphalein test. The patient in case 14, when first seen, about a week after the onset of jaundice induced by an arsphenamine hepatitis, had a marked retention of dye. Six days later, when the jaundice was clearing, the modified dextrose tolerance test produced a severe hypoglycemia at the end of two hours, and in the galactose test, done three days before, 8 Gm. was excreted (the normal excretion being 3 Gm. or less). Five months later, there was no retention of dye at the end of one-half hour, and 3.4 Gm. of galactose was excreted in five hours, but the modified dextrose tolerance test still showed a definite hypoglycemia (29 mg. per one hundred cubic centimeters).

COMMENT

It is apparent from the foregoing data that the modified dextrose tolerance test produced a terminal hypoglycemia in nine of ten patients who gave no evidence of hepatic disease. It is also clear that there is no essential difference between the response of this group and that of the group in which frank hepatic damage was present. The curve in case 9 (duodenal ulcer), for example, can be practically superimposed on that in case 13 (syphilitic hepatitis). The only distinction between the two groups is that in the cases with hepatic damage the peaks of the curves were higher, and the minimal blood sugar levels were, on the whole, somewhat lower and were reached sooner, than in most of the normal cases. No explanation for the wide variation in the

maximal blood sugar levels is apparent. Althausen noted the same phenomenon in his cases, and he also offered no explanation. This feature, however, is irrelevant to the present study. The point to be emphasized is that a definite hypoglycemia was produced in practically all patients who were considered to have normal livers, as well as in those whose livers were diseased.

Case 14, that of a patient with arsphenamine hepatitis, presents perhaps one of the strongest arguments against the validity of the modified dextrose tolerance test. This patient, who at the onset of his illness exhibited evidence of severe hepatic damage by the dye, the galactose and the dextrose-insulin tests, showed a normal reaction to the bromsulphalein test and an almost normal reaction to the galactose test five months later but still exhibited marked hypoglycemia with the modified dextrose tolerance test. Had hypoglycemia not developed in most of the normal cases, one might infer that the results in this case indicate that the modified dextrose tolerance test is more sensitive than the other tests and can detect lesser degrees of hepatic damage. In the face of the results in persons with normal livers, however, such an inference is not justified.

Results somewhat similar to those in case 14 were obtained in cases 12 and 13. The dye tests gave normal results, but the modified dextrose tolerance tests showed definite hypoglycemia, the reverse of the condition reported by Althausen as diagnostic of toxic cirrhosis. Althausen, in discussing his findings in this disease, attributed the impairment of ability to excrete dye, coincident with a normal dextrose-insulin test, to the presence of areas of regenerated liver parenchyma able to carry on carbohydrate metabolism normally, but unable to excrete dye or bile because of the absence of available bile channels. If one assumes, with Althausen, that the excretion of dye and carbohydrate metabolism are both functions of the polygonal cells of the liver, one would be justified in expecting that if in any condition there is enough hepatic parenchyma having access to the biliary system to give a normal excretion of dye, the same parenchyma should be capable of performing its normal metabolic functions as regards carbohydrates. Applying this hypothesis to cases 12, 13 and 14, one finds that there is indeed a normal excretion of dye, but that the expected normality of carbohydrate metabolism, as judged by the dextrose-insulin test, is not forthcoming. One must conclude, therefore, either that (*a*) the tests are inadequate, or (*b*) there exists some degree of differential hepatic function. The adequacy of the dye tests, as implied, is still open to question. It has already been shown, however, that the modified

dextrose tolerance test is unreliable, for hypoglycemic reactions occurred in the normal cases of this series (groups I and II) just as in the abnormal ones (group III). Consequently, although the existence of differential hepatic function is a possibility, it is not proved by the method under consideration.

From the practical point of view, therefore, it seems obvious that the modified dextrose tolerance test cannot be regarded as a satisfactory test of the metabolic activity of the diseased liver. On the same basis, there is no justification for the theory that the simultaneous presence of a "normal" modified dextrose tolerance test and an "abnormal" dye test in a person with disease of the liver indicates the existence of a toxic cirrhosis. Any attempt at differential diagnosis on such a basis is invalidated by the fact that this carbohydrate test frequently gives the same results in normal persons as in those with proved hepatic disease.

From the theoretical standpoint also, the dextrose-insulin test in its present form is open to several objections. In the first place, it is a common experience to find that in normal persons the ordinary dextrose tolerance test, in which 100 Gm. of dextrose without insulin is given, is often followed by a drop in blood sugar to a point below the fasting level. McClellan and Wardlaw,[5] in a review of various conditions leading to hypoglycemia, cite the ingestion of carbohydrate as one of them, and refer to the work of Folin and Berglund,[6] of Hamman and Hirschman,[7] of Foster,[8] of Stenström[9] and of John,[10] all of whom have reported a drop in blood sugar to below fasting levels, in some cases as low as from 31 to 45 mg., in from two to four hours after the ingestion of varying amounts of dextrose by normal subjects.

If, then, the ingestion of 100 Gm. of dextrose alone is frequently followed by hypoglycemia, it seems logical to suppose that in a test in which 20 units of insulin is given to a fasting subject and covered by only 50 Gm. of dextrose, low blood sugar levels and insulin reactions would be encountered with even greater frequency. That such is the case is borne out by the preceding studies.

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6. Folin, Otto, and Berglund, H.: Some New Observations and Interpretations with Reference to the Transportation, Retention and Excretion of Carbohydrates, J. Biol. Chem. **51**:213 (March) 1922.

7. Hamman, L., and Hirschman, I. I.: Studies on Blood Sugar: IV. Effects upon the Blood Sugar of Repeated Ingestion of Glucose, Bull. Johns Hopkins Hosp. **30**:306 (Oct.) 1919.

8. Foster, G. L.: Studies on Carbohydrate Metabolism: I. Some Comparisons of Blood Sugar Concentration in Venous Blood and in Finger Blood, J. Biol. Chem. **55**:291 (Feb.) 1923.

9. Stenström, T.: Hypoglykämische Reaktion nach Funktionsprobe mit Glykose, Deutsches Arch. f. klin. Med. **157**:216 (Oct.) 1927.

10. John, H. J.: Hyperinsulinism, Surg., Gynec. & Obst. **44**:190 (Feb.) 1927.

In the second place, the metabolism of dextrose is a complex process, and is susceptible of modification by a number of factors other than those directly connected with the liver. Althausen and his colleagues [1] mention diabetes mellitus, thyrotoxicosis, myasthenia gravis and diabetes insipidus as being conditions which should theoretically interfere with the estimation of carbohydrate metabolism. McClellan and Wardlaw,[5] in a review of the literature on hypoglycemia, list, among other things, physical exhaustion, renal glycosuria, idiopathic hyperinsulinism, Addison's disease, progressive muscular dystrophy, scleroderma, bronchial asthma and changes in the nervous system as conditions in which low blood sugar has been found during fasting. It is not expected that the frequency of occurrence of these abnormal states in disease of the liver would be sufficient to interfere seriously with the general adoption of the dextrose-insulin test; but the presence of hypoglycemia in these conditions reconfirms the fact, already well established, that the metabolism of dextrose and often its expression in values of blood sugar are closely linked with the function of organs other than the liver and the pancreas, especially the thyroid, pituitary and suprarenal glands, and probably the muscles. It is interesting to note in this connection that Folin and Berglund,[6] in 1922, during a study of the effects of the ingestion of dextrose in man, observed that the hyperglycemia so produced was augmented by the emotional reaction of a nervous subject, who fainted during a venipuncture. Emotional hyperglycemia has since become a well recognized entity, and constitutes another possible variable in any study of dextrose metabolism in man.

Finally, if one were to waive all the foregoing considerations, there would still remain the well known fact that there is a wide variation among normal persons with respect to tolerance for insulin. The response of an obese subject, for example, to a certain dose of insulin, is likely to be different from that of a malnourished one. It is possible that the modified dextrose tolerance test, based on the administration of a certain amount of dextrose and a certain amount of insulin per pound of body weight or per unit of surface area, might yield more satisfactory results than could be expected from its administration according to the present technic. This possibility, however, because of the many variable factors already mentioned, is considered to be remote.

SUMMARY

1. The modified dextrose tolerance test of the function of the liver, as described by Althausen, Gunther, Lagen and Kerr, was performed on ten patients who were considered to have normal livers at the time of examination, and on four patients with frank hepatic disease.

2. Of the ten normal patients, nine responded to the test by a drop in blood sugar to points considerably below the critical level for normal reactions, and showed symptoms and signs of hypoglycemia.

3. Of the four patients with frank hepatic disease, three responded by definite chemical and clinical hypoglycemia.

4. There was no essential difference between the behavior of the normal and the abnormal groups.

CONCLUSION

The modified dextrose tolerance test in its present form is not a satisfactory measure of the metabolic function of the liver.

Correspondence

"THE RELATION OF WITHDRAWAL OF CEREBROSPINAL FLUID TO THE BODY TEMPERATURE"

To the Editor:—I should like to call attention to the fact that the article published by Dr. Alfred Gordon of Philadelphia, entitled, "The Relation of Withdrawal of Cerebrospinal Fluid to the Body Temperature," in the ARCHIVES OF INTERNAL MEDICINE (**44**:263 [Aug.] 1929) is, as regards comment, summary, conclusions and references, merely a condensed and slightly altered translation of my own paper entitled, "Die Beziehungen von pathologischen und experimentellen Veränderungen der physikalischen Liquorverhältnisse des Menschen zur Körpertemperatur," published in the *Zeitschrift für die gesamte Neurologie und Psychiatrie* (**105**:347, 1926).

Dr. Gordon has also published a similar translation, "La relation du liquide céphalo-rachidien avec la température du corps humain," in the *Revue neurologique* (**2**:44, 1929).

H. A. STRECKER, M.D., Birmingham, England.

To the Editor:—Years before Dr. Strecker's article appeared in the *Zeitschrift für die gesamte Neurologie and Psychiatrie* I became interested in the subject under discussion, as stated in the introductory remarks of my article. From the extensive references published in Dr. Strecker's article one can see how many men made observations on this subject. I kept on collecting personal cases of neuropsychiatric character until I had accumulated 250, and only then did I publish my observations. In medicine many men may work on the same problem simultaneously in different parts of the world, and they may arrive at the same conclusions. The problem of the walls of the third ventricle or, preferably, the hypothalamic area as a thermoregulatory center has been suggested time and again clinically and experimentally. My personal views on the subject ran and still run in the same direction. The case of Dr. Strecker and mine merely show a coincidence and similarity of observation. I read extensively on this subject, and among a large literature I selected only a few references, which were mentioned in my article. They happened to be among the many references which Dr. Strecker used for his article. Since my few references are the property of the entire scientific world, what is wrong if I happened to peruse them in the library? As I had decided to make a systematic study of the 250 lumbar and ventricular punctures, I devised my own method of observation as to the frequency of punctures and the registration of temperature. A careful perusal of Dr. Strecker's article will show that his method is decidedly different from mine. My conclusions, as well as those of many other authors, and those of Dr. Strecker are similar, of course, but they are not altogether identical. My fate may be the same as that of many others who have worked on the same problem. Dr. Strecker may make the same reproach to others. The tracings in my article are not identical with those in his article. Tracings were necessary, and if they remind one of those in Dr. Strecker's article, it does not make them identical. My contribution was purely a clinical one and cannot be compared with that of Dr. Strecker in extent and completeness, for the reason that he viewed not only the clinical side, but also the experimental angle. He also treated the subject of hypothermia, which I have mentioned only casually. Should it be held against me if two men from different lands happen to think alike and draw the same conclusions on the same subject even though their methods are somewhat similar?

ALFRED GORDON, M.D., Philadelphia.

Book Reviews

Funktionelle Pathologie. By Gustav von Bergmann, with the assistance of Dr. Martin Goldner. Price, 18.60 marks. Pp. 425, with 74 illustrations. Berlin: Julius Springer, 1932.

The author is the well known professor of internal medicine and director of the Second Medical Clinic of the University of Berlin. The volume is a collection and summary of his clinical work and that of a group of co-workers published in various journals, textbooks and proceedings of scientific meetings over a period of more than twenty years. He states that the points of view and conclusions may be regarded as representative of a school of modern German medicine.

The first six chapters deal with the gastro-intestinal, pancreatic and biliary systems. These are followed by a chapter each on inflammation and allergy, obesity and malnutrition and hyperthyroidism and the thyrotic constitution. Four chapters are devoted to disturbances and diseases of the vascular system. Chapter 14 contains a discussion of the visceral nervous system, and is followed by a chapter called "Diagnostic Reformation"; the latter will be discussed in more detail presently. The last three chapters are entitled, respectively, "Psychophysical Reactions," "Regulations" and "Causation and Teleology." The second chapter of this group is a consideration of the regulatory processes of the various functions of the body, such as those of temperature, blood pressure, blood sugar and acid-base equilibrium, through nervous reflexes and humoral control. The third one is in large part a philosophic dissertation on the author's attitude toward modern medicine and its future possibilities. Such entities as phthisis, carcinoma and syphilis are not discussed per se, and there was no intention that the volume should serve as a *Lehrbuch*.

Barring some interesting digressions, chiefly of a roentgenologic and therapeutic nature, the theme which permeates the major portion of this work is succinctly expressed by the title "Functional Pathology." To disturbance of function the author attributes the genesis of many symptoms, conditions and eventual disease states heretofore ascribed to pathologic states or interpreted as psychoneurotic manifestations. Invariably the surgeon or the pathologist is not able to demonstrate this functional lesion anatomically. In further illustration of this theme, some of the organs will be considered. The colon is the first in order because, from roentgenoscopic examination of the larger movements of the colon of man under both normal and abnormal conditions, von Bergmann has learned to understand dyskinesia, and so far as this organ is concerned dyskinesia may be defined as a disturbance of normal coordination of the different larger and smaller intestinal movements and of tonus, in brief, a neuromuscular disturbed action. He regards constipation, "irritable" colon, ulcerative colitis, pseudo-appendicitis and appendicitis, diverticulosis and diverticulitis as the end-results of long-standing antecedent dysfunction, either latent or active. Mucous colitis is classified as a purely allergic disease, styled bronchial asthma of the colon, the result of neuromuscular and neurosecretory (parasympathetic) excitation.

The clinical attempt to apply functional pathology consciously at the bedside had its inception in the study of gastric disorder and disease. In these two chapters on the stomach again appears von Bergmann's familiar neurogenic theory of the causation of ulcer, which, briefly stated, apart from the factors of constitutional and personal characteristics, is that a disharmony of the involuntary nervous system exists, resulting in vascular or muscular spasm, focal ischemia, capillary and venous stasis, submucosal hemorrhage and eventual erosion and ulceration of the gastric wall to a variable depth by the digestive action of the gastric juice. Von Bergmann maintains that it is now possible to demonstrate the development of an ulcer from the functional disturbances to the anatomic product, which, in his opinion, is a comparatively new conception in pathology. Jores was one of the first to conceive this, with respect to the red granular kidney as a product of the functional lesion,

hypertension. Observations on the forms of dyskinesia of the excretory ducts of the larger digestive glands (for example, the extrahepatic bile ducts, pancreatic ducts) take up two chapters, and such forms of dyskinesia are considered the basis for clinical symptoms and eventual disease.

With regard to the circulatory system the author's observations include studies of the neuromuscular behavior of the arterioles, and finally of the veins. This resulted in his "dynamic conception," namely, that hypertonus, decompensation and local vascular disturbances are the results of disturbed function. He apparently considers spasm as the primary factor in the occurrence of apoplexy, myomalacia of the heart, coronary disease, intermittent claudication and the symptom of cold fingers in older persons. On the surface, this conception might seem fantastic, but von Bergmann enlists a wealth of clinical, experimental and pathologic evidence to support it.

In addition to neural disharmony, humoral types of disharmony are recognized. The vegetatively stigmatized are understood to be those of hyperthyroid constitution. The frequency of latent disease is stressed. As a consequence, there resulted the postulate "Abbau der reinen Organneurosen." All this induced decisive diagnostic and therapeutic changes. In the author's opinion, the demarcation between organic and functional has disappeared. He emphasizes the point that a disturbance of function, or functional disturbance, is by no means identical with a neurotic or psychic disturbance. However, the proper consideration of normal and abnormal psychic factors is an important part of medical art.

The chapter on diagnostic reformation is largely devoted to a consideration of those diseases which in the author's opinion are not diagnosed frequently enough. These are the diseases with a background of functional disturbance, and include latent hypertension, latent circulatory decompensation, disturbances induced by small herniations through the esophageal hiatus, with or without cardiospasm, and the so-called "epiphrenal complex." To these are added: gastritis; duodenal and gastrojejunal ulcer; forms of hepatopathy, such as fatty liver, latent hepatic cirrhosis, latent cholangeitis and latent cholecystopathy; subacute pancreatitis; diverticula throughout the gastro-intestinal tract, particularly those of the papilla of Vater, with resultant inflammatory disease of the extrahepatic and pancreatic ducts; latent disturbances or insufficiency of the glands of internal secretion; allergic inflammatory states involving the extremities, skin, liver, intestine, gallbladder, stomach and blood vessels, and latent infections. The common diagnoses which von Bergmann considers are too often erroneous and which should be discouraged are: those of visceral neurosis, especially of the heart and stomach; ptosis and atony of all or a portion of the organs of the digestive tract; ptosis of the kidney; intestinal spasm; painful adhesions; "rheumatic" pains and intercostal neuralgia; angina abdominis; vagotonia, and sympathicotonia.

One would think that an English translation of this volume would prove an inspiration and a challenge to every American physician. Aside from the exposition of an interesting thesis, the volume contains many instructive clinical facts, a review of much original research, descriptions of functional tests more or less unfamiliar to Americans and a number of rational and novel therapeutic hints. The chapter entitled "Psychophysiche Verhaltungsweisen" could be read profitably by every clinician and neuropsychiatrist. The author's basic conception is either right or entirely wrong, and should it prove to be the former, the work of this school might be considered as epochal in the annals of clinical medicine, as Virchow's was in cellular pathology. That all are not in accord with some of his views is evidenced by articles appearing in the current German literature. For example, Sauerbruch and his school are by no means in accord with the dicta laid down by von Bergmann and his associates concerning hiatus hernia. Sauerbruch is not ready to accept the author's conception of the epiphrenal symptom complex. However, we are inclined to agree with von Bergmann as our own experience is more or less in agreement with that of the author, particularly with reference to the incidence, roentgenoscopic phenomena and the symptomatology engendered by subdiaphragmatic hernia. Von Krecke likewise insists that complaints of the right upper abdominal quadrant may be, and frequently are, purely psychogenic

in origin. That ulcerative colitis is usually the end-result of long-standing antecedent colonic dysfunction will also be disputed by many authorities in this country. The same may be said of diverticulosis of the colon. At any rate, the volume is a brilliant and thought-provoking contribution to contemporary German medical literature.

Hospitals and Child Health: Hospitals and Dispensaries, Convalescent Care, Medical Social Service. Reports of the Subcommittees on Hospitals and Dispensaries, Clifford G. Grulee, Chairman; Convalescent Care, Adrian V. S. Lambert, Chairman; Medical Social Service, Ida M. Cannon, Chairman. Cloth. Price, $2.50. Pp. 279. New York: Century Company, 1932.

This volume, which is one of the publications of the White House Conference on Child Health and Protection, presents the material secured by a number of committees which studied the particular problems of hospitals and dispensaries, convalescent care and medical social service in relation to children.

The first section of the book is devoted to the study of hospitals and dispensaries in the United States. The two chief purposes of a hospital, the care of the sick and the education of professional and lay groups, form the basis for the questionnaires that were sent to the hospitals of the United States by the committee. The results of the study are revealing and interesting. It was found that the number of hospitals in the country is more than adequate. Also, although the number of beds assigned definitely for children is not proportionate to the entire bed capacity, many of the answers to the questionnaires stated that the hospitals had room for as many children's beds as are needed, although there is no special pediatric department. However, other vital matters, such as conditions of entrance, the area served, the types of cases accepted and whether there is a special pediatric staff, were not satisfactory. The children's hospitals and special hospitals seem lacking also in many essentials. The answers to questions on dispensaries lead one to believe that there are too few dispensaries, although in the ones existing the right attitude toward the patient and the control and prevention of disease seems to be present. At the end of the section is a list of recommendations which naturally follow as a result of the study.

The second section is concerned with the reports of the subcommittee on convalescent care, a discussion of the present conditions and recommendations for what should be done. Convalescence is defined as being "that period following an attack of illness during which an individual is unable to return to what would be for him a normal routine of life and during which he does not require the constant, thoughtful supervision of a physician, and it implies that he will be able to return to his normal life if relieved of life's burdens for a reasonable length of time."

The homes now used as convalescent institutions apparently are located in proper surroundings, but the reports indicate a general inadequacy so far as fire hazards, length of stay and number of beds available are concerned. That there is financial waste when a child who might be in a convalescent bed is taking up a more expensive bed in a hospital for the acutely ill cannot be questioned. Under the suggestions of what should be done, the subcommittee offers several solutions. The necessity for specialized homes and the necessity for more interest in convalescent care by the individual physicians are among the recommendations for giving better and more complete convalescent care. Foster homes are discussed, and a workable plan is suggested by Dr. Henry Dewight Chapin, who is founder and director of the Speedwell Society of New York City. At the end of the section, tables are given which are a result of the questionnaires sent out by the subcommittee.

The section on medical social service is the longest report of the three. This study includes the amount of medical social service, where located, the interpretations of the functions of medical social service, the organization, the educational equipment, the present facilities for training the workers, the relationship of medical social service to medicine, nursing and social work and recommendations based on the findings.

The recommendations among many things emphasize the necessity of encouraging medical social service and of improving this service through a discriminating analysis of accumulated experience. The section includes extracts from discussions by persons who understand the need for the coordination of all phases in carrying out the best care of the patient.

Poliomyelitis: A Survey Made Possible by a Grant from the International Committee for the Study of Infantile Paralysis, organized by Jeremiah Milbank. Price, $6. Pp. 562. Baltimore: Williams & Wilkins Company, 1932.

Jeremiah Milbank of New York in 1928 wished to contribute something as a layman to the battle against poliomyelitis. After conferences with men eminently qualified to advise and plan, the International Committee for the study of Infantile Paralysis was organized, with Dr. William H. Park as chairman. Its membership was made up of the heads of the medical departments of a number of universities and laboratories here and abroad, each of whom would be free to choose those phases of the problem in which he was most interested, but all cooperating in an effort to have the sum of their work broadly inclusive of the whole field of research in this disease. Mr. Milbank's personal interest in the work was sustained and sincere, and his financial contributions over a four year period totaled $280,000.

The present volume summarizes all the important work done on poliomyelitis. About 8,000 references were consulted, of which a bibliography of almost 800 references is given. About 80 of these references are to papers by members of the committee. The data are presented in the following seven sections: "Historical Summary," "Etiology," "Resistance and Immunity," "Symptomatology," "Treatment," "Pathology" and "Epidemiology."

A critical review of the great mass of knowledge collected would be superfluous. A few important conclusions may be noted. In 1840 Heine was the first to establish the disease as a clinical entity. The many subsequent classifications have been modified, and the following five types are recognized: abortive, nonparalytic, subcortical paralytic (the usual), cerebral or encephalitic (rare) and ataxic (very rare). "Probably not more than 25 per cent of all cases of poliomyelitis that can be diagnosed develop paralysis. The case fatality is usually from 10 to 15 per cent. As practically all fatal cases are in the paralyzed group, the number surviving with paralysis is much less than 25 per cent of the total number of cases. Of the cases with paralysis a complete restitution of function will take place in a goodly number and a partial restitution in the remainder. There is, so far as we know, no danger of mental defects and there is but slight indication that the child will be more susceptible to other nervous disorders." The need for some simple, but definite and absolute, diagnostic test remains. No safe method of active immunization has yet been developed. Passive immunization yields greater promise. An addendum on page 529 calls attention to the Bradford, Pa., epidemic of September, 1932, in which, of thirteen hundred children inoculated with parental whole blood, not one contracted the disease.

Regarding etiology, it is stated that "there are some workers who, while not denying that poliomyelitis is caused by a filtrable virus, believe that this virus is only one stage in the life cycle of the agent, which appears in another stage as a pleomorphic streptococcus. No such cycle has yet been demonstrated with certainty for any of the other viruses and a very considerable amount of work has been done which in our minds is sufficient to disprove any etiological relationship between the streptococcus and poliomyelitis." (The bearing of the recent work of Kendall on this question is not discussed.) The period of incubation is at least seven days.

This volume is of inestimable value in summarizing with dependable thoroughness all present information on poliomyelitis. The great amount of time and effort which went into its preparation will mean an immense saving to all future contributors to this problem. The medical profession and the public owe a large debt of gratitude to Mr. Milbank.

Herzneurosen und moderne Kreislauftherapie. IX. Fortbildungs-Lehrgang in Bad Nauheim, Sept. 16-18, 1932. Published by the Physicians Association of Bad Nauheim. Price, 10 marks. Pp. 159, with 22 illustrations. Dresden: Theodore Steinkopf, 1932.

This excellent and instructive brochure is divided into three main sections: (1) the cardiac neuroses, consisting of five lectures, (2) cardiovascular therapy, comprising six contributions and (3) miscellaneous, with four discussions by eminent physicians on cardiovascular anatomy, endocarditis and heart failure, pulmonary insufficiency and its reciprocal relationship to the vascular system and the rôle of the kidney in the circulation.

The reviewer has read carefully and with pleasure and interest the fifteen lectures, and aside from those in which microscopic and other means of demonstration were utilized in explaining the data, it would indeed be difficult to decide whether one was more complete or instructive than another.

The enthusiasm of Professor Groedel for the therapeutic effects of carbon dioxide baths in quite an imposing series of cardiac and vascular diseases, including hypertension and hypertrophy, is perhaps rather surprising, but one must remember that he is connected with Bad Nauheim.

The general dietetic and special drug therapy for heart diseases is amply covered by Schloss, Rosin, Schoen and Siebeck. Their discussions are masterpieces of clarity and completeness without the tendency to become prolix. These men are conservative and up-to-date.

The pharmacology and therapy of camphor and camphor substitutes is discussed by Professor Schoen, and the relatively weak and slow absorption of camphor in the form commonly used is minutely compared with the rapid response obtained from metrazol, pyridine-carbonic acid diethyl-amide and 3-methyl-5-isopropyl 2.3-cyclohexone. The latter substance is said to be chemically similar to camphor, whereas the other two substances are entirely different. While camphor and 3-methyl-5-isopropyl 2.3-cyclohexone are insoluble in water, pyridine-carbonic acid diethyl-amide and metrazol are soluble and are adapted both to oral and to intravenous administration and have in practice performed good service in cases in which rapid central stimulation was demanded, for example, in collapse following anesthesia and severe infections, morphine and carbon monoxide poisoning, usually with suicidal intent, and following an overdose of one of the many proprietary hypnotics on the market.

The chapters devoted to the anatomy of the nervous innervation of the heart and large vessels and to the more intimate structures of the vascular walls contain points of interest which could doubtless be fully understood only by seeing the diagrams and slides. The same impression is left by reading Herzog's treatment of the problem of endocarditis; viz., it cannot be appreciated without at the same time viewing his preparations.

The kidney and its relation to the cardiovascular system are handled by Professor Becker in the final chapter of the book. The logical reasoning, together with the scientific acumen which the writer displays in marshaling his facts and in making his deductions, can be appraised only by reading the original text.

This book contains much valuable material for every one specially interested in heart diseases or in any other clinical subject in which a knowledge of cardiovascular ailments is desirable; and in what branch of clinical medicine is it not?

Physical Chemistry of Living Tissues and Life Processes. By R. Beutner, M.D., Ph.D., Professor of Pharmacology, School of Medicine, University of Louisville. Price, $5. Pp. 337, with 79 figures. Baltimore: Williams & Wilkins Company, 1933.

This book, by a professor of pharmacology, fills a much-needed gap in modern biologic and medical education. Its fundamental outlook savors of Jacques Loeb and the Woods Hole of his day. It is the attempt of a biologist to apply physics and chemistry to cells. In this respect its purpose is distinctly futuristic, because the application of fundamental laws to the physiology of cells is in its beginning. Much of the volume will, no doubt, have to be rewritten as knowledge of cytologic

physics and chemistry increases. Nevertheless, the work recommends itself to the student of biology and medicine, especially to the student of experimental medicine, because its point of view is distinctly that of the coming generation.

The book introduces life "as a scientific problem" and proposes the finding of suitable artificial models for the study of phenomena peculiar to living organisms. The first section discusses membranes, electrolytes and osmosis. Permeability and body fluids are here expounded. The second section deals with surface forces and crystallization. Emulsions and artificial cells are described which exhibit ameboid movement and even respiration. The third section enumerates electrical currents in tissues. Electrode potentials and phase boundary potentials are considered in the light of action currents and the current injury. Much of this material would be termed biophysics by modern physical chemists.

To the medical practitioner twenty years out of medical school, this book will seem not only mystical but probably also unintelligible. Nevertheless, present-day premedical eduction is such that the author is justified in stating that the "text of this book can be readily understood by the average medical student." The more complicated mathematics is relegated to an appendix. Reference footnotes and diagrams abound in simple but instructive form. Adequate indexes of subjects and authors are appended.

This short volume should appeal to all who take pleasure in the understanding of vital mechanism.

Some Factors in the Localisation of Disease in the Body. By Harold Burrows, C.B.E., F.R.C.S., Assistant at the Research Institute of the Cancer Hospital (Free), Consulting Surgeon to the War Memorial Hospital, Gosport; Late Consulting Surgeon, His Majesty's Forces; Late Hunterian Professor, Royal College of Surgeons. Cloth. Price, $4.50. Pp. 299, with 8 colored plates. New York: William Wood & Company, 1932.

This is a unique work that wanders in a highly speculative field and at the same time makes practical use of its material. The title is a bit misleading. One would suspect that the book dealt with the reasons why diseases selected certain portions of the body for their point of attack. This is true, but the author also discusses the limitation of disease processes, secundum artem, using the knowledge gained in studying the various biologic and physiologic tissue changes both in experimental animals and in patients. The study of these changes takes the author into the fields of biology, physics, chemistry and electricity. With much of this work as a basis, new conceptions must be built up concerning certain ill-understood diseases. The author mentions in this connection epilepsy, puerperal sepsis and chronic arthritis.

The book deals first with the localization of foreign proteins, dyes, pigments, syphilis, bacteria, virus and cancer. It then deals with the factors that promote and limit specific localization in the tissues. The final division discusses the practical application of the facts gleaned from the study of localization and its attendant factors.

As stated, the book is highly speculative, and there are many statements that cannot at present be well supported. The whole work, however, has a convincing atmosphere that must serve as a stimulus for further investigation along similar lines.

Tactique opératoire du pancréas et de la rate. By J. Okinczyc and L. Aurousseau. Price, 75 francs. Pp. 267. Paris: Gaston Doin & Cie, 1933.

A great deal of interesting material is compressed into this volume, and while a description of surgical technic is the primary purpose, one learns about the general problems of pancreatic and splenic disease as well. Of especial value is the analysis of surgical experience in the past which has led up to present methods. The book is well illustrated and indexed, and the bibliography is especially rich in French titles. The book should prove of great value to the American reader who wishes to familiarize himself with French practice in connection with the surgery of the spleen and the pancreas.